(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number
WO 02/066470 A1

(51) International Patent Classification[7]: C07D 409/12, 409/14, 213/82, 401/12, 401/14, 409/04, 413/14, 417/14, 405/14, 405/12

(21) International Application Number: PCT/US02/00743

(22) International Filing Date: 11 January 2002 (11.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/261,339	12 January 2001 (12.01.2001)	US
60/323,764	19 September 2001 (19.09.2001)	US
10/046,681	10 January 2002 (10.01.2002)	US

(71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oak, CA 91320-1799 (US).

(72) Inventors: CHEN, Guoqing; 515 Oakbury Court, Thousand Oaks, CA 91360 (US). ADAMS, Jeffrey; 2915 Venezia Lane, Thousand Oaks, CA 91362 (US). BEMIS, Jean; 256 Appleton Street, Arlington, MA 02476 (US). BOOKER, Shon; 587 North Ventu Park Road, Suite E, Newbury Park, CA 91320 (US). CAI, Guolin; 2382 Whitechaple Place, Thousand Oaks, CA 91362 (US). CROGHAN, Michael; 1108 Dover Lane, Ventura, CA 93001 (US). DIPIETRO, Lucian; 37 Centennial Avenue, Gloucester, MA 01930 (US). DOMINGUEZ, Celia; 963 Cedarcliff Court, Thousand Oaks, CA 91362 (US). ELBAUM, Daniel; 25 Sherrin Road, Newton, MA 02462 (US). GERMAIN, Julie; 28 Woods Avenue, Somerville, MA 02144 (US). GEUNS-MEYER, Stephanie; 59 Fountain Street, Medford, MA 02155 (US). HANDLEY, Michael; 215 Ford Avenue, Ventura, CA 93003 (US). HUANG, Qi; 12308 Willow Forest Drive, Moorpark, CA 93021 (US). KIM, Joseph, L.; 20 Green Way, Wayland, MA 01778 (US). KIM, Tae-Seong; 1580 Dover Avenue, Thousand Oaks, CA 91360 (US). KISELYOV, Alexander; 174 Washingotn Street, Apartment 3Q, Jersey City, NJ 07302 (US). OUYANG, Xiaohu; 132-20 Maple Avenue, Flushing, NY 11355 (US). PATEL, Vinod, F.; 3 Mossy Lane, Acton, MA 01720 (US). SMITH, Leon, M.; 33 Julie Court, Sommerset, NJ 08873 (US). STEC, Markian; 978 Arrasmith Lane, Filmore, CA 93015 (US). TASKER, Andrew; 561 Granite Hills Street, Simi Valley, CA 93065 (US). XI, Ning; 565 Timberwood Avenue, Thousand Oaks, CA 91360 (US). XU, Shimin; 1890 West Hillcrest Drive, Number 406, Newbury Park, CA 91320 (US). YUAN, Chester, Chenguang; 1416 Geyser Court, Newbury Park, CA 91320 (US).

(74) Agents: ODRE, Steven, M. et al.; Amgen Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED ALKYLAMINE DERIVATIVES AND METHODS OF USE

(57) Abstract: Selected heterocyclic compounds are effective for prophylaxis and treatment of diseases, such as angiogenesis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable derivatives thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

WO 02/066470 A1

SUBSTITUTED ALKYLAMINE DERIVATIVES AND METHODS OF USE

FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer and angiogenesis-related disorders.

BACKGROUND OF THE INVENTION

Protein kinases represent a large family of proteins which play a central role in the regulation of a wide variety of cellular processes, maintaining control over cellular function. A partial list of such kinases includes abl, Atk, bcr-abl, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. Inhibition of such kinases has become an important therapeutic target.

Certain diseases are known to be associated with deregulated angiogenesis, for example ocular neovascularization, such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including rheumatoid arthritis), or other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and neoplastic diseases, for example so-called solid tumors and liquid tumors (such as leukemias).

At the center of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth, and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as Vascular Endothelial Growth Factor"(VEGF; originally termed 'Vascular Permeability Factor", VPF), along with its cellular receptors (see G. Breier et al., Trends in Cell Biology, 6, 454-6 (1996)).

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein related to "Platelet-Derived Growth Factor" (PDGF); it is produced by normal cell lines and tumor cell lines; is an endothelial cell-specific mitogen; shows angiogenic activity in *in vivo* test systems (e.g. rabbit cornea); is chemotactic for endothelial cells and monocytes; and induces plasminogen activators in endothelial cells, which are involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as "Placenta Growth Factor"(PlGF) and VEGF-C.

VEGF receptors (VEGFR) are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types of VEGF receptor are known, e.g. VEGFR-1 (also known as flt-1), VEGFR-2 (also known as KDR), and VEGFR-3.

A large number of human tumors, especially gliomas and carcinomas, express high levels of VEGF and its receptors. This has led to the hypothesis that the VEGF released by tumor cells stimulates the growth of blood capillaries and the proliferation of tumor endothelium in a paracrine manner and through the improved blood supply, accelerate tumor

growth. Increased VEGF expression could explain the occurrence of cerebral edema in patients with glioma. Direct evidence of the role of VEGF as a tumor angiogenesis factor *in vivo* is shown in studies in which VEGF expression or VEGF activity was inhibited. This was achieved with anti-VEGF antibodies, with dominant-negative VEGFR-2 mutants which inhibited signal transduction, and with antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumor cell lines *in vivo* as a result of inhibited tumor angiogenesis.

Angiogenesis is regarded as an absolute prerequisite for tumors which grow beyond a diameter of about 1-2 mm; up to this limit, oxygen and nutrients may be supplied to the tumor cells by diffusion. Every tumor, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: 1) Inhibition of the growth of vessels, especially capillaries, into avascular resting tumors, with the result that there is no net tumor growth owing to the balance that is achieved between cell death and proliferation; 2) Prevention of the migration of tumor cells owing to the absence of blood flow to and from tumors; and 3) Inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels. See R. Connell and J. Beebe, Exp. Opin. Ther. Patents, 11, 77-114 (2001).

VEGF's are unique in that they are the only angiogenic growth factors known to contribute to vascular hyperpermeability and the formation of edema. Indeed, vascular hyperpermeability and edema that is associated with

the expression or administration of many other growth factors appears to be mediated via VEGF production.

Inflammatory cytokines stimulate VEGF production. Hypoxia results in a marked upregulation of VEGF in numerous tissues, hence situations involving infarct, occlusion, ischemia, anemia, or circulatory impairment typically invoke VEGF/VPF-mediated responses. Vascular hyperpermeability, associated edema, altered transendothelial exchange and macromolecular extravasation, which is often accompanied by diapedesis, can result in excessive matrix deposition, aberrant stromal proliferation, fibrosis, etc. Hence, VEGF-mediated hyperpermeability can significantly contribute to disorders with these etiologic features. As such, regulators of angiogenesis have become an important therapeutic target.

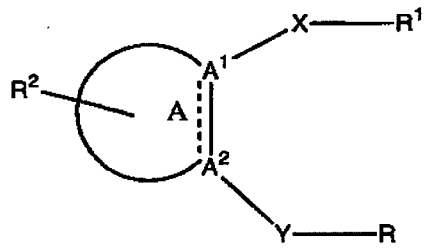
Schipper US patent 3,226,394, issued Dec. 28, 1965, describes anthranilamides as CNS depressants. Japanese patent JP2000256358 describes pyrazole derivatives that block the calcium release-activated calcium channel. EP application 9475000, published 6 October 1999, describes compounds as PGE_2 antagonists. PCT publication WO96/41795, published 27 December 1996, describes benzamides as vasopressin antagonists. WO01/29009 describes aminopyridines as KDR inhibitors. WO01/30745 describes anthranilic acids as CGMP phosphodiesterase inhibitors. WO00/02851, published 20 Jan 2000 describes arylsulfonylamnoaryl amides as guanylate cyclase activators. WO98/45268 describes nicotinamide derivatives as PDE4 inhibitors. WO98/24771 describes benzamides as vasopressin antagonists.

US Patent No. 5,532,358, issued July 2, 1996, describes the preparation of 2-(cyclopropylamino)-N-(2-methoxy-4-methyl-3- pyridinyl)-3-pyridinecarboxamide as an intermediate for HIV inhibitors. Triazine-substituted amines are described for their aggregating ability (J. Amer.

Chem. Soc., 115, 905-16 (1993). Substituted imidazolines were tested for their antidepressant activity in Ind. J. Het. Chem., 2, 129-32 (1992). N-(4-Pyridyl)anthranilic amides were described in Chem Abstr. 97:109837 (1981). PCT publication WO99/32477, published 1 July 1999, describes anthranilamides as anti-coagulants. US patent 6,140,351 describes anthranilamides as anti-coagulants. PCT publication WO99/62885, published 9 December 1999, describes 1-(4-aminophenyl)pyrazoles as antiinflammatories. PCT publication WO00/39111, published 6 July 2000, describes amides as factor Xa inhibitors. PCT publication WO00/39117, published 6 July 2000, describes heteroaromatic amides as factor Xa inhibitors. PCT publication WO00/27819, published 18 May 2000, describes anthranilic acid amides as VEGF inhibitors. PCT publication WO00/27820 published 18 May 2000, describes N-aryl anthranilic acid amides as VEGF inhibitors. 7-Chloroquinolinylamines are described in FR2168227 as antiinflammatories. WO01/55114, published 2 Aug. 2001, describes nicotinamides for the treatment of cancer. WO01/55115, published 2 Aug. 2001, describes nicotinamides as inducers of apoptosis. WO01/85715, published 15 November 2001, describes substituted pyridines and pyrimidines as anti-angiogenesis agents. PCT publication WO01/85691 published 15 November 2001, describes anthranilic amides as VEGF inhibitors. PCT publication WO01/85671 published 15 November 2001, describes anthranyl amides as VEGF inhibitors. PCT publication WO01/81311 published 1 November 2001, describes anthranilic amides as VEGF inhibitors. However, compounds of the current invention have not been described as inhibitors of angiogenesis such as for the treatment of cancer.

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating cancer and angiogenesis is defined by Formula I



I

wherein each of A^1 and A^2 is independently C, CH or N;

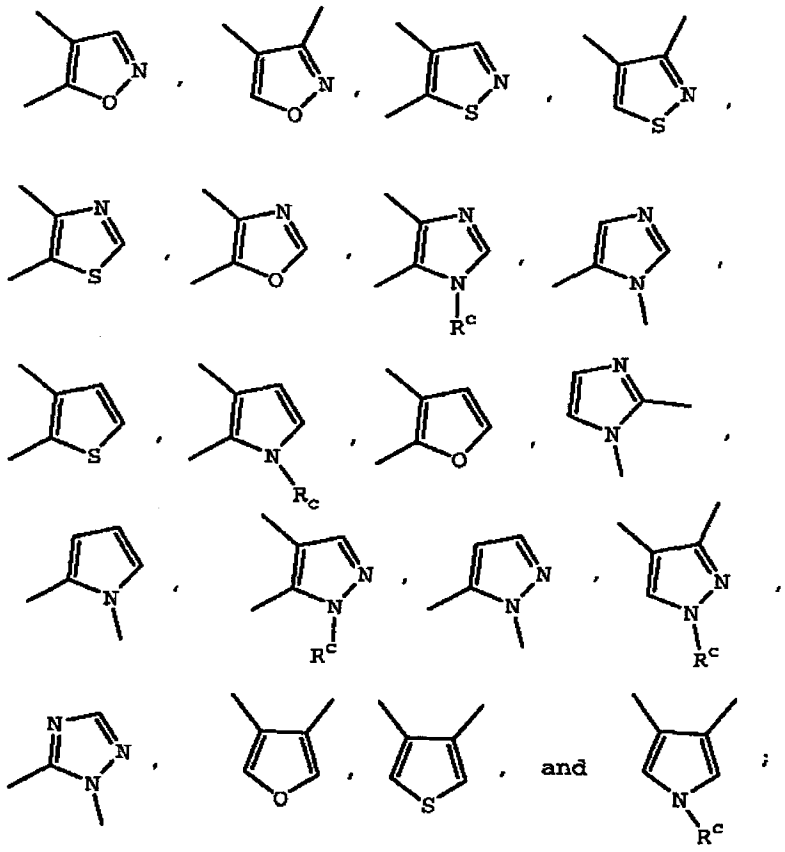
wherein ring A is selected from

a) 5- or 6-membered partially saturated heterocyclyl, preferably dihydropyran, dihydrothienyl, dihydrofuryl, oxo-dihydrofuryl, pyrrolinyl, dihydrothiazolyl, dihydro-oxazolyl, dihydro-isothiazolyl, dihydro-isoxazolyl, imidazolinyl and pyrazolinyl,

b) 5- or 6-membered heteroaryl, preferably

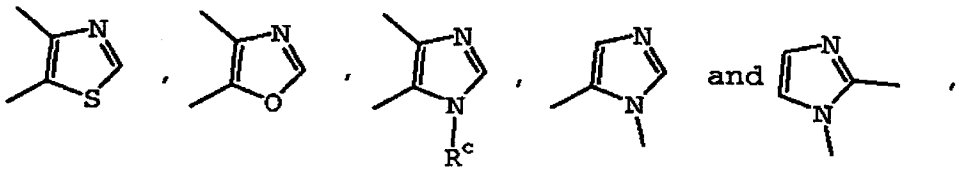
I) 5-membered heteroaryl selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl,

even more preferably 5-membered heteroaryl selected from

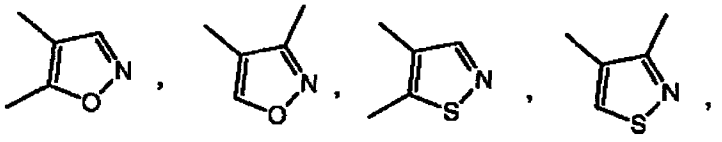


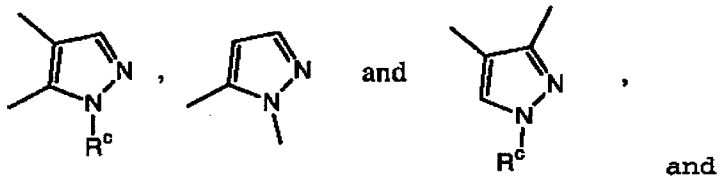
specifically

A)



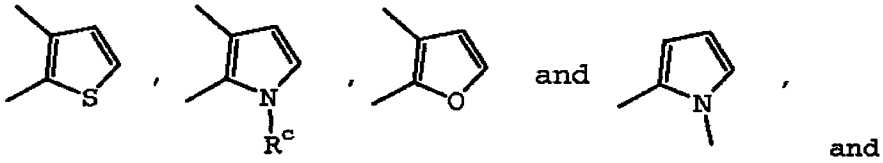
B)





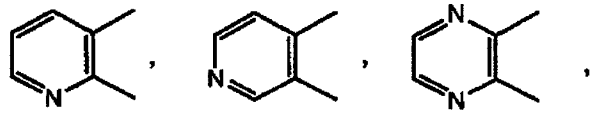
and

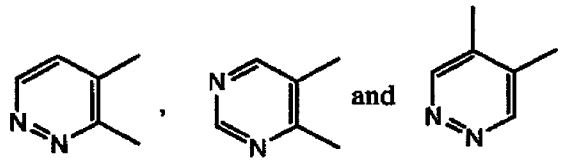
C)



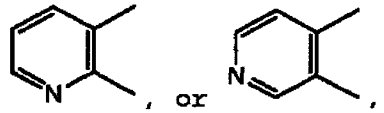
and

II) preferably 6-membered heteroaryl selected from pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl,
even more preferably 6-membered heteroaryl selected from





more specifically



c) 9-, 10- or 11-membered fused partially saturated heterocyclyl
preferably tetrahydroquinolinyl,

d) 9- or 10-membered fused heteroaryl,
preferably

i) fused 9-membered fused heteroaryl selected from benzothienyl, benzothiazolyl, indolyl,

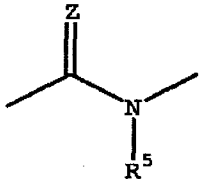
benzimidazolyl, benzoxazolyl, benzofuryl, indazolyl and isoindolyl, and

ii) fused 10-membered heteroaryl selected from quinolyl, isoquinolyl, naphthpyridinyl, quinoxalinyl and quinazolinyl,

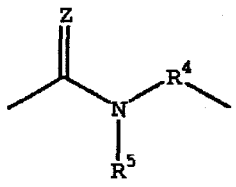
e) naphthyl, and

f) 4-, 5- or 6-membered cycloalkenyl, preferably 5-membered cycloalkenyl, more preferably cyclopentadienyl or cyclopentenyl;

wherein X is selected from

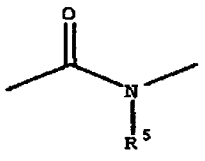


and

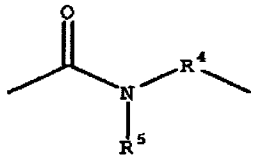


,

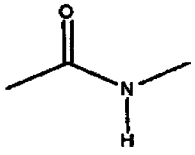
preferably X is selected from



and



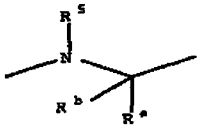
,



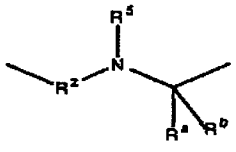
more preferably X is ;

wherein Z is oxygen or sulfur;

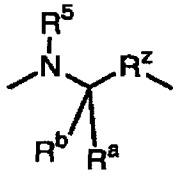
wherein Y is selected from



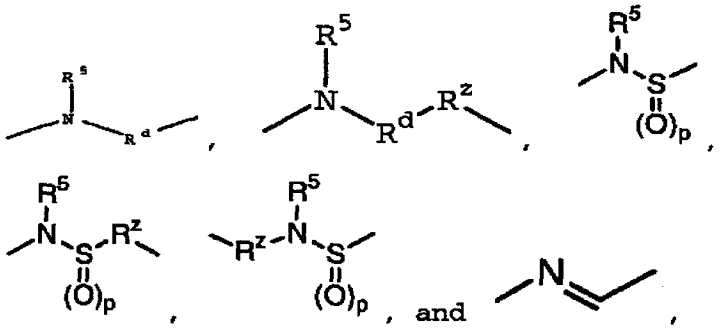
,



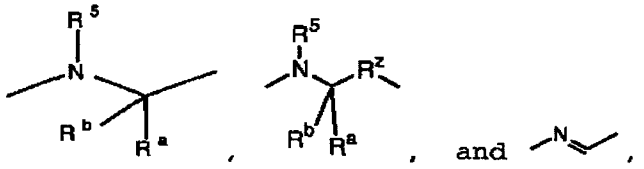
,



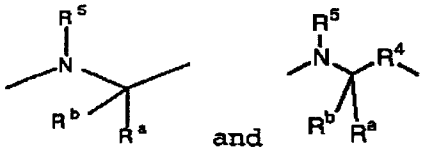
,



preferably Y is selected from



more preferably Y is selected from



even more preferably Y is -NH-CH_2-;

wherein R^a and R^b are independently selected from H, halo, cyano and C_{1-4}-alkyl substituted with R^2, or wherein R^a and R^b together form C_3-C_4 cycloalkyl,

preferably H, halo, cyano and C_{1-2}-alkyl substituted with R^2, or wherein R^a and R^b together form C_3-C_4 cycloalkyl,

more preferably H, halo and C_1-C_2-alkyl,

even more preferably H;

wherein R^z is selected from C_1-C_4 alkylenyl, where one of the CH_2 groups may be substituted with an oxygen atom or an -NH-,

preferably C_1-C_2 alkylenyl, where one of the CH_2 groups may be substituted with an oxygen atom or an -NH-

more preferably C_1-C_2 alkylenyl;

wherein R^d is cycloalkyl,

preferably C_3-C_6 cycloalkyl;

wherein R is selected from

a) substituted or unsubstituted 5-6 membered heterocyclyl,
preferably substituted or unsubstituted 5-6 membered heteroaryl comprising one or more nitrogen atoms,
more preferably 4-pyrazolyl, triazolyl, 4-pyridyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 4-pyridazinyl, or 6-pyridazinyl,
even more preferably 4-pyridyl, 4-pyrimidinyl and 4-pyridazinyl,
even more preferably 4-pyridyl, and

b) substituted or unsubstituted fused 9-, 10- or 11-membered heterocyclyl,
preferably substituted or unsubstituted 9-10 membered fused heteroaryl comprising one or more nitrogen atoms,
more preferably indazolyl, quinolinyl, isoquinolinyl, or quinazolinyl,
even more preferably indazolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 4-isoquinolyl, 5-isoquinolyl, and 6-isoquinolyl,

wherein substituted R is substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-SO_2R^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, lower alkyl substituted with R^2, cyano, nitro, lower alkenyl and lower alkynyl;
preferably halo, $-OR^3$, $-SR^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, $-NR^3C(O)NR^3R^3$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, C_{1-2}-alkyl, cyano, C_{1-2}-hydroxyalkyl, nitro and C_{1-2}-haloalkyl;

wherein R^1 is selected from

a) substituted or unsubstituted 6-10 membered aryl, preferably phenyl, naphthyl, indenyl, or tetrahydronaphthyl, more preferably phenyl,

b) substituted or unsubstituted 5-6 membered heterocyclyl, preferably 5-6 membered heteroaryl, more preferably thienyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, furyl, or pyrrolyl,

c) substituted or unsubstituted 9-10 membered fused heterocyclyl, preferably 9-10 membered fused heteroaryl, more preferably indazolyl, indolyl, 2,1,3-benzothiadiazolyl, isoquinolyl, quinolyl, tetrahydroquinolyl, benzodioxanyl, or quinazolinyl,

d) cycloalkyl, and

e) cycloalkenyl

wherein substituted R^1 is substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-NH(C_1-C_4$ alkylenyl$R^{14})$, $-SO_2R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, optionally substituted cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, lower alkyl substituted with R^2, cyano, nitro, lower alkenyl and lower alkynyl,

preferably R^1 is unsubstituted or substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-SO_2R^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-NH(C_1-C_2$ alkylenyl$R^3)$, $-(C_1-C_2$ alkylenyl$)NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$,

optionally substituted cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-2}-alkylenyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, C_{1-2}-alkyl, cyano, C_{1-2}-hydroxyalkyl, nitro and C_{1-2}-haloalkyl, more preferably R^1 is unsubstituted or substituted with one or more substituents selected from chloro, fluoro, bromo, methoxy, phenyloxy, benzyl, methylthio, methyl, ethyl, trifluoromethyl, difluoromethyl, pentafluoroethyl, hydroxymethyl, cyano, carboxy, aminocarbonyl, methylcarbonyl, amino, methylamino, cyclopropyl, cyclohexyl, piperidinyl, morpholinyl, N-methylpiperazinyl, N-ethylpiperazinyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, methylaminothiocarbonyl, N-methylamino-methylenyl, optionally substituted phenyl, N,N-diethylamino, or N,N-dimethylamino;

wherein R^2 is one or more substituents independently selected from H, halo, $-OR^3$, oxo, $-SR^3$, $-CO_2R^3$, $-COR^3$, $-CONR^3R^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl, lower carboxyalkyl, nitro, lower alkenyl, lower alkynyl, lower aminoalkyl, lower alkylaminoalkyl and lower haloalkyl, preferably R^2 is one or more substituents independently selected from H, halo, $-OR^3$, oxo, $-SR^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted 5-6

membered heterocyclyl, optionally substituted phenyl, C_{1-2}-alkyl, cyano, C_{1-2}-hydroxyalkyl, C_{1-3}-carboxyalkyl, nitro, C_{2-3}-alkenyl, C_{2-3}-alkynyl and C_{1-2}-haloalkyl;

wherein R^3 is selected from H, lower alkyl, phenyl, 5-6 membered heterocyclyl, C_3-C_6 cycloalkyl, and lower haloalkyl,

preferably H, C_{1-2}-alkyl, phenyl, C_3-C_6 cycloalkyl, and C_{1-2}-haloalkyl,

more preferably H, methyl, phenyl, cyclopropyl, cyclohexyl, and trifluoromethyl;

wherein R^4 is independently selected from C_{2-4}-alkylenyl, C_{2-4}-alkenylenyl and C_{2-4}-alkynylenyl, where one of the CH_2 groups may be substituted with an oxygen atom or an -NH-,

preferably C_{2-3}-alkylenyl where one of the CH_2 groups may be substituted with an oxygen atom or an -NH-,

more preferably C_2-C_3 alkylenyl;

wherein R^5 is selected from H, lower alkyl, phenyl and lower aralkyl,

preferably H, methyl or ethyl;

wherein R^6 is selected from H or C_{1-6}-alkyl,

preferably H or C_{1-2} alkyl; and

wherein R^c is selected from H, methyl and optionally substituted phenyl;

wherein R^{14} is selected from H, phenyl, 5-6 membered heterocyclyl and C_3-C_6 cycloalkyl;

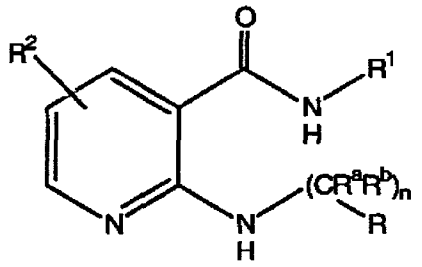
wherein p is 0 to 2, preferably p is 2;

and pharmaceutically acceptable salts thereof;

provided A is not naphthyl when X is -C(O)NH- and when R^1 is phenyl when Y is -$NHCH_2$- and when R is 4-pyridyl; further provided A is not pyridyl when X is -C(O)NH- and when R^1 is 4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl when Y is -$N(CH_3)$- and when R is 4-methylpiperidinyl; further provided A is not pyridyl when X is -C(O)NH- and when Y is -$NHCH_2$ - and when R is 4-pyridylpiperidin-4-yl, 1-tertbutylpiperidin-

4-yl, 1-isopropylpiperidin-4-yl or 1-cycloalkylpiperidin-4-yl; further provided A is not pyridyl when X is -C(O)NH- and when R^1 is 4-[3-(3-pyridyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl when Y is $-NHCH_2-$ and when R is 4-pyridyl; and further provided R is not unsubstituted 2-thienyl, 2-pyridyl or 3-pyridyl.

The invention also relates to compounds of Formula II



II

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,

preferably 4-pyridyl, pyrimidinyl, triazolyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,

where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,

preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy,

preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

C_{1-6}-haloalkoxy,

C_{1-6}-carboxyalkyl,

unsubstituted or substituted aryl and

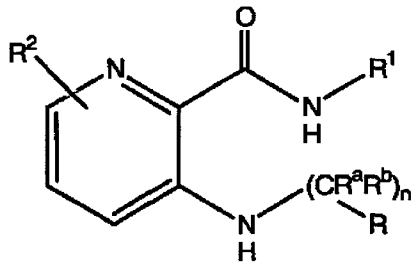
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula III



III

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,

preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,

where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,

preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy,

preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

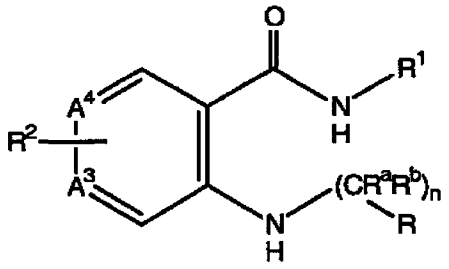
C_{1-6}-alkyl,
C_{1-6}-haloalkyl,
C_{1-6}-alkoxy,
C_{1-6}-haloalkoxy,
C_{1-6}-carboxyalkyl,
unsubstituted or substituted aryl and
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula IV



IV

wherein A^3 is selected from CR^2 and N;

wherein A^4 is selected from CR^2 and N; provided one of A^3 and A^4 is not CR^2;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,

preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,

where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,

preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy,

preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl,

methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

C_{1-6}-haloalkoxy,

C_{1-6}-carboxyalkyl,

unsubstituted or substituted aryl and

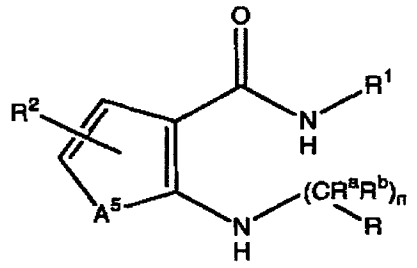
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula V



V

wherein A^5 is selected from S, O and NR^6;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,
preferably H;
wherein n is 0-2;
preferably 1-2;
wherein R is selected from
a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and
b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,
preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,
where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,
preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;
wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,
preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,
wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted

phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy, preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

C_{1-6}-haloalkoxy,

C_{1-6}-carboxyalkyl,

unsubstituted or substituted aryl and

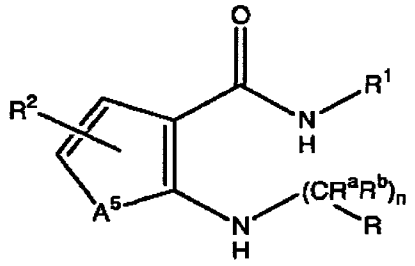
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula VI



VI

wherein A^5 is selected from S, O and NR^6;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,

preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,

where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,

preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl,

tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy,

preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

C_{1-6}-haloalkoxy,

C_{1-6}-carboxyalkyl,

unsubstituted or substituted aryl and

unsubstituted or substituted 5-6 membered heteroaryl;

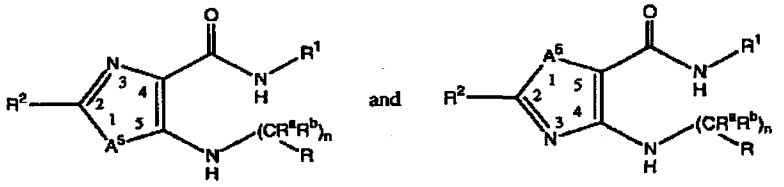
preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted

phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula VII



VIIa and VIIb **VII**

wherein A^5 is selected from S, O and NR^6;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$, preferably H;

wherein n is 0-2; preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl, preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl, where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy, preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy,

preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

C_{1-6}-haloalkoxy,

C_{1-6}-carboxyalkyl,

unsubstituted or substituted aryl and

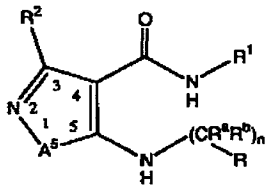
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

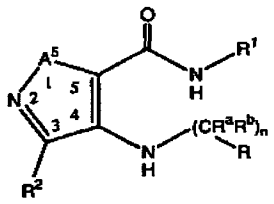
wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula VIII



and



VIIIa VIIIb

wherein A^5 is selected from S, O and NR^6;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,

preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,

where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,

preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy,

preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

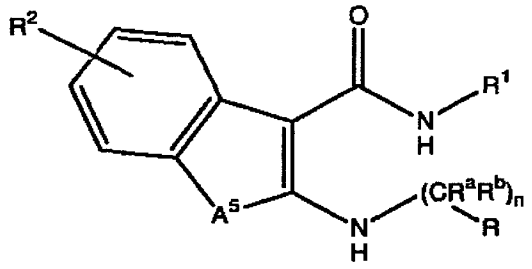
C_{1-6}-alkyl,
C_{1-6}-haloalkyl,
C_{1-6}-alkoxy,
C_{1-6}-haloalkoxy,
C_{1-6}-carboxyalkyl,
unsubstituted or substituted aryl and
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula IX



IX

wherein A^5 is selected from S, O and NR^6;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl, preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl, where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy, preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy, preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl,

ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

C_{1-6}-haloalkoxy,

C_{1-6}-carboxyalkyl,

unsubstituted or substituted aryl and

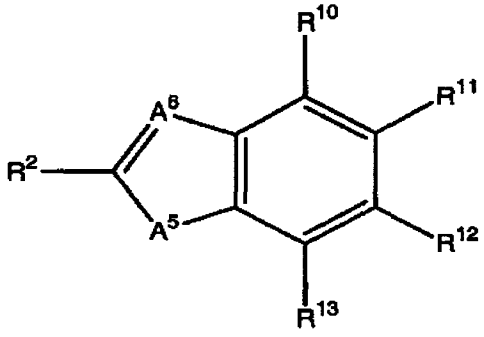
unsubstituted or substituted 5-6 membered heteroaryl;

preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula X



X

wherein A^5 is selected from S, O and NR^6;

wherein A^6 is selected from N and CR^2;

wherein R^a and R^b are independently selected from H, halo, C_{1-4}-alkyl and $-N(R^6)_2$,

preferably H;

wherein n is 0-2;

preferably 1-2;

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, and

b) unsubstituted or substituted 9- or 10-membered fused nitrogen-containing heteroaryl,

preferably 4-pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl or quinozalinyl,

where R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl and C_{1-6}-alkoxy,

preferably substituted with one or more substituents selected from chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl, 5-6-membered heteroaryl and 9-10 membered fused heteroaryl,

preferably unsubstituted or substituted phenyl, tetrahydronaphthyl, naphthyl, isoquinolyl, quinolyl, pyridyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, naphthyridinyl, quinozalinyl, tetrahydroquinolinyl, indazolyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl, or benzthiazolyl,

wherein R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally

substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, C_{1-6}-haloalkoxy, optionally substituted phenyloxy, benzyl, optionally substituted 5-6 membered heterocyclyl-C_1-C_2-alkylenyl, optionally substituted heteroaryl, optionally substituted heteroaryloxy, C_{1-6}-haloalkyl, and C_{1-6}-alkoxy, preferably chloro, fluoro, amino, hydroxy, cyclohexyl, phenylmethyl, morpholinylmethyl, methylpiperdinylmethyl, methylpiperazinylmethyl, ethyl, propyl, trifluoromethyl, phenyloxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,

halo,

C_{1-6}-alkyl,

C_{1-6}-haloalkyl,

C_{1-6}-alkoxy,

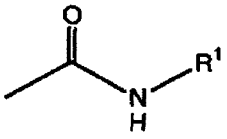
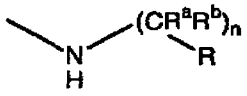
C_{1-6}-haloalkoxy,

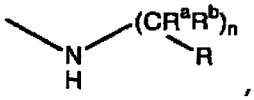
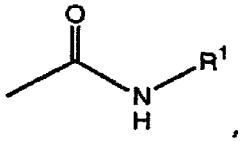
C_{1-6}-carboxyalkyl,

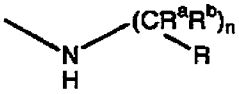
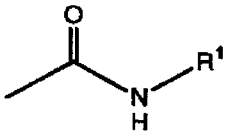
unsubstituted or substituted aryl and unsubstituted or substituted 5-6 membered heteroaryl;

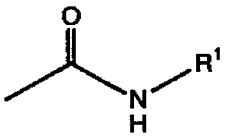
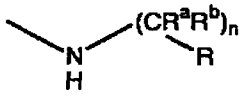
preferably one or more substituents independently selected from H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl;

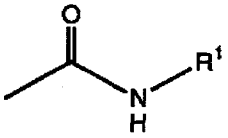
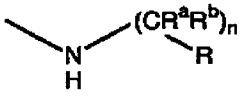
wherein

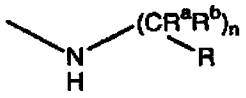
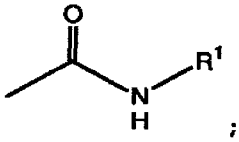
a) R^{10} is  , R^{11} is  , R^{12} is H, and R^{13} is H; or

b) R^{10} is  , R^{11} is  , R^{12} is H, and R^{13} is H; or

c) R^{10} is H, R^{11} is  , R^{12} is  , and R^{13} is H; or

d) R^{10} is H, R^{11} is  , R^{12} is  , and R^{13} is H; or

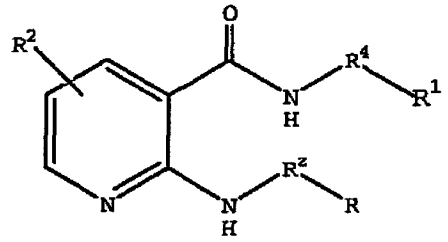
e) R^{10} is H, R^{11} is H, R^{12} is  , and R^{13} is  ; or

f) R^{10} is H, R^{11} is H, R^{12} is  , and R^{13} is  ; and

wherein R^6 is H or C_{1-2}-alkyl;

and pharmaceutically acceptable isomers and salts thereof.

The invention also relates to compounds of Formula II'



II'

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl,

preferably 4-pyridyl, 3-pyridyl, 2-pyridyl, pyrimidinyl, triazolyl, and pyridazinyl,

more preferably 4-pyridyl, and

b) unsubstituted or substituted 9- or 10-membered fused heterocyclyl

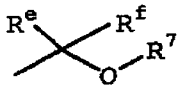
preferably indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, benzotriazolyl, 2,3-dihydrobenzofuryl, 2-oxo-1,2-dihydroquinol-7-yl, naphthyridinyl and quinozalinyl,

where substituted R is substituted with one or more substituents selected from halo, amino, hydroxy, oxo, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkylamino, optionally substituted heterocyclyl-C_{1-6}-alkyl, C_{1-6}-alkylamino-C_{2-4}-alkynyl, C_{1-6}-alkylamino-C_{1-6}-alkoxy, C_{1-6}-alkylamino-C_{1-6}-alkoxy-C_{1-6}-alkoxy, and optionally substituted heterocyclyl-C_{2-4}-alkynyl,

preferably chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, dimethylaminopropynyl, 1-

methylpiperdinylmethoxy,
dimethylaminoethoxyethoxy, methoxy and ethoxy;
wherein R^1 is selected from unsubstituted or substituted
aryl, preferably phenyl, tetrahydronaphthyl, indanyl,
indenyl, and naphthyl,
cycloalkyl, preferably cyclohexyl,
5-6 membered heteroaryl, preferably isoxazolyl,
pyrazolyl, thiazolyl, thiadiazolyl, thienyl, pyridyl,
pyrimidinyl, and pyridazinyl, and
9-10 membered bicyclic and 13-14 membered tricyclic
heterocyclyl, preferably 1,2-dihydroquinolyl,
1,2,3,4-tetrahydro-isoquinolyl, isoquinolyl,
quinolyl, indolyl, isoindolyl, 2,3-dihydro-1H-
indolyl, naphthyridinyl, quinozalinyl,
benzo[d]isothiazolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-
aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-
a]isoquinolyl, tetrahydroquinolinyl, indazolyl,
2,1,3-benzothiadiazolyl, benzodioxanyl,
benzothienyl, benzofuryl, dihydro-benzimidazolyl,
benzimidazolyl, benzoxazolyl and benzthiazolyl;
wherein substituted R^1 is substituted with one or more
substituents selected from halo, C_{1-6}-alkyl, optionally
substituted C_{3-6}-cycloalkyl, optionally substituted
phenyl, optionally substituted phenyl-C_1-C_4-alkylenyl, C_{1-2}-haloalkoxy, optionally substituted 4-6 membered
heterocyclyl-C_1-C_4-alkylenyl, optionally substituted 4-6
membered heterocyclyl-C_2-C_4-alkenylenyl, optionally
substituted 4-6 membered heterocyclyl, optionally
substituted phenyloxy, optionally substituted 4-6
membered heterocyclyloxy, optionally substituted 4-6
membered heterocyclyl-C_{1-4}-alkyloxy, optionally
substituted 4-6 membered heterocyclylsulfonyl, optionally
substituted 4-6 membered heterocyclylamino, optionally
substituted 4-6 membered heterocyclylcarbonyl, optionally

substituted 4-6 membered heterocyclyl-C_{1-4}-alkylcarbonyl, C_{1-2}-haloalkyl, C_{1-4}-aminoalkyl, nitro, amino, -NHC(O)NH_2, alkylcarbonylamino, hydroxy, oxo, cyano, aminosulfonyl, C_{1-2}-alkylsulfonyl, halosulfonyl, C_{1-4}-alkylcarbonyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkoxy, C_{1-3}-alkylamino-C_{1-3}-alkoxy-C_{1-3}-alkoxy, C_{1-4}-alkoxycarbonyl, C_{1-4}-alkoxycarbonylamino-C_{1-4}-alkyl, C_{1-4}-hydroxyalkyl,



and C_{1-4}-alkoxy,

preferably bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-

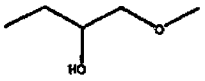
methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;

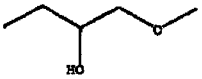
wherein R^2 is one or more substituents independently selected from

H,
halo,
hydroxy,
amino,
C_{1-6}-alkyl,
C_{1-6}-haloalkyl,
C_{1-6}-alkoxy,
C_{1-2}-alkylamino,
aminosulfonyl,

C_{3-6}-cycloalkyl,
cyano,
C_{1-2}-hydroxyalkyl,
nitro,
C_{2-3}-alkenyl,
C_{2-3}-alkynyl,
C_{1-6}-haloalkoxy,
C_{1-6}-carboxyalkyl,
5-6-membered heterocyclyl-C_{1-6}-alkylamino,
unsubstituted or substituted phenyl and
unsubstituted or substituted 5-6 membered heterocyclyl;

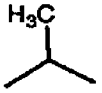
preferably H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, oxo, dimethylamino, aminosulfonyl, cyclopropyl, cyano, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, morpholinylethylamino, propynyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl;

wherein R^4 is selected from a direct bond, C_{1-4}-alkyl, and  ,



preferably a direct bond, ethyl, butyl, and ;

wherein R^z is selected from C_{1-2}-alkyl, C_{2-6}-branched alkyl, C_{2-4}-branched haloalkyl, amino-C_{1-4}-alkyl and C_{1-2}-alkylamino-C_{1-2}-alkyl,

preferably methylenyl, ethylenyl,  , and aminoethylenyl;

wherein R^e and R^f are independently selected from H and C_{1-2}-haloalkyl,

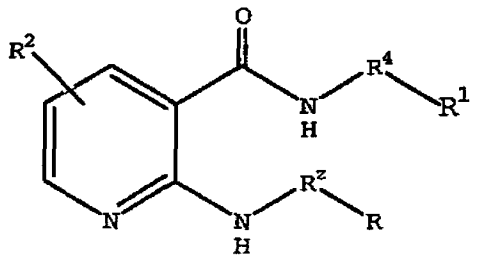
preferably trifluoromethyl; and

wherein R^7 is selected from H, C_{1-3}-alkyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-3}-alkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-C_1-C_3-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-3}-alkoxy-C_{1-2}-alkyl and C_{1-3}-alkoxy-C_{1-3}-alkoxy-C_{1-3}-alkyl;

provided R^2 is not H, or provided R^1 is not heteroaryl or aryl or provided R is substituted with optionally substituted heterocyclyl-C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkylamino, optionally substituted heterocyclyl-C_{1-6}-alkyl, C_{1-6}-alkylamino-C_{2-4}-alkynyl, C_{1-6}-alkylamino-C_{1-6}-alkoxy, C_{1-6}-alkylamino-C_{1-6}-alkoxy-C_{1-6}-alkoxy, or optionally substituted heterocyclyl-C_{2-4}-alkynyl, or R^1 is substituted with optionally substituted phenyloxy, optionally substituted 5-6 membered heterocyclyloxy, optionally substituted 5-6 membered heterocyclylsulfonyl, optionally substituted 5-6 membered heterocyclylamino, optionally substituted 5-6 membered heterocyclylcarbonyl, optionally substituted 5-6 membered heterocyclyl-C_{1-4}-alkylcarbonyl, C_{1-3}-alkylamino-C_{1-3}-alkoxy, or C_{1-3}-alkylamino-C_{1-3}-alkoxy-C_{1-3}-alkoxy; further provided R is not 3-pyridyl when R^z is CH_2;

and pharmaceutically acceptable isomers and derivatives thereof.

The invention also relates to compounds of Formula XI



XI

wherein R is selected from

a) unsubstituted or substituted 5- or 6-membered nitrogen-containing heteroaryl, preferably 4-pyridyl, 3-pyridyl, 2-pyridyl, pyrimidinyl, triazolyl, and pyridazinyl, more preferably 4-pyridyl, and

b) unsubstituted or substituted 9- or 10-membered fused heteroaryl preferably indolyl, isoindolyl, indazolyl, quinolyl, isoquinolyl, benzotriazolyl, naphthyridinyl and quinozalinyl,

where substituted R is substituted with one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkylamino, optionally substituted heterocyclyl-C_{1-6}-alkyl, C_{1-6}-alkylamino-C_{2-4}-alkynyl, C_{1-6}-alkylamino-C_{1-6}-alkoxy, C_{1-6}-alkylamino-C_{1-6}-alkoxy-C_{1-6}-alkoxy, and optionally substituted heterocyclyl-C_{2-4}-alkynyl, preferably chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, dimethylaminopropynyl, 1-methylpiperdinylmethoxy, dimethylaminoethoxyethoxy, methoxy and ethoxy;

wherein R^1 is selected from unsubstituted or substituted aryl,

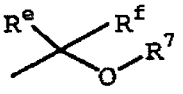
cycloalkyl,
5-6 membered heteroaryl and
9-10 membered bicyclic and 13-14 membered tricyclic heterocyclyl,

preferably phenyl, tetrahydronaphthyl, indanyl, indenyl, naphthyl, cyclohexyl, isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, pyridyl, pyrimidinyl, pyridazinyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, isoquinolyl, quinolyl, indolyl, isoindolyl, 2,3-dihydro-1H-indolyl, naphthyridinyl, quinozalinyl, benzo[d]isothiazolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, tetrahydroquinolinyl, indazolyl, 2,1,3-benzothiadiazolyl, benzodioxanyl, benzothienyl, benzofuryl, dihydro-benzimidazolyl, benzimidazolyl, benzoxazolyl and benzthiazolyl,

specifically 4-6 membered saturated or partially un-saturated monocyclic heterocyclyl,
9-10 membered saturated or partially un-saturated bicyclic heterocyclyl, and
13-14 membered saturated or partially un-saturated tricyclic heterocyclyl,

more specifically 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 2,3-dihydro-1H-indolyl, benzo[d]isothiazolyl, dihydro-benzimidazolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, and tetrahydroquinolinyl,

wherein substituted R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, optionally substituted phenyl-C_1-C_4-alkylenyl,

C_{1-2}-haloalkoxy, optionally substituted 4-6 membered heterocyclyl-C_1-C_4-alkyl, optionally substituted 4-6 membered heterocyclyl-C_2-C_4-alkenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted phenyloxy, optionally substituted 4-6 membered heterocyclyloxy, optionally substituted 4-6 membered heterocyclyl-C_1-C_4-alkoxy, optionally substituted 4-6 membered heterocyclylsulfonyl, optionally substituted 4-6 membered heterocyclylamino, optionally substituted 4-6 membered heterocyclylcarbonyl, optionally substituted 5-6 membered heterocyclyl-C_{1-4}-alkylcarbonyl, C_{1-2}-haloalkyl, C_{1-4}-aminoalkyl, nitro, amino, hydroxy, oxo, cyano, aminosulfonyl, C_{1-2}-alkylsulfonyl, halosulfonyl, C_{1-4}-alkylcarbonyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkoxy, C_{1-3}-alkylamino-C_{1-3}-alkoxy-C_{1-3}-alkoxy, C_{1-4}-alkoxycarbonyl, C_{1-4}-alkoxycarbonylamino-C_{1-4}-alkyl, C_{1-4}-hydroxyalkyl,  and C_{1-4}-alkoxy, preferably bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-

Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;

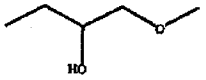
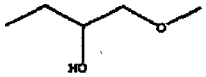
wherein R^2 is one or more substituents independently selected from

H,
halo,
hydroxy,
amino,
C_{1-6}-alkyl,
C_{1-6}-haloalkyl,
C_{1-6}-alkoxy,
C_{1-2}-alkylamino,
aminosulfonyl,
C_{3-6}-cycloalkyl,
cyano,
C_{1-2}-hydroxyalkyl,
nitro,
C_{2-3}-alkenyl,
C_{2-3}-alkynyl,
C_{1-6}-haloalkoxy,
C_{1-6}-carboxyalkyl,
5-6-membered heterocyclyl-C_{1-6}-alkylamino,
unsubstituted or substituted phenyl and
unsubstituted or substituted 5-6 membered heterocyclyl,

preferably H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, oxo, dimethylamino, aminosulfonyl, cyclopropyl, cyano, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, morpholinylethylamino, propynyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl,

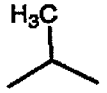
specifically chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, oxo, dimethylamino, aminosulfonyl, cyclopropyl, cyano, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy,

trifluoromethoxy, carboxymethyl, morpholinylethylamino, propynyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, furanyl, pyridyl, imidazolyl, and pyrazolyl;

wherein R^4 is selected from a direct bond, C_{1-4}-alkyl, and  , 

preferably a direct bond, ethyl, butyl, and ;

wherein R^z is selected from C_{1-2}-alkyl, C_{2-6}-branched alkyl, C_{2-4}-branched haloalkyl, amino-C_{1-4}-alkyl and C_{1-2}-alkylamino-C_{1-2}-alkyl,

preferably methylenyl, ethylenyl,  , and aminoethylenyl;

wherein R^e and R^f are independently selected from H and C_{1-2}-haloalkyl,

preferably trifluoromethyl; and

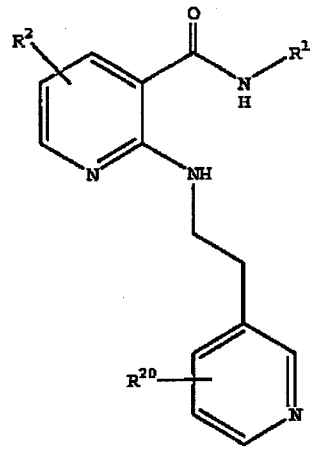
wherein R^7 is selected from H, C_{1-3}-alkyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-3}-alkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-C_1-C_3-alkyl, C_{1-3}-alkoxy-C_{1-2}-alkyl and C_{1-3}-alkoxy-C_{1-3}-alkoxy-C_{1-3}-alkyl;

provided R^1 is substituted with optionally substituted phenyloxy, optionally substituted 4-6 membered heterocyclyloxy, optionally substituted 4-6 membered heterocyclyl-C_{1-4}-alkoxy, optionally substituted 4-6 membered heterocyclylsulfonyl, optionally substituted 4-6 membered heterocyclylamino, optionally substituted 4-6 membered heterocyclylcarbonyl, optionally substituted 4-6 membered heterocyclyl-C_{1-4}-

alkylcarbonyl, C_{1-3}-alkylamino-C_{1-3}-alkoxy, or C_{1-3}-alkylamino-C_{1-3}-alkoxy-C_{1-3}-alkoxy; further provided R is not 3-pyridyl when R^5 is CH_2;

and pharmaceutically acceptable isomers and derivatives thereof.

The invention also relates to compounds of Formula XII



XII

wherein R^1 is selected from unsubstituted or substituted

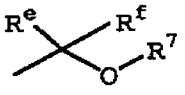
aryl, preferably phenyl, tetrahydronaphthyl, indanyl, indenyl, and naphthyl,

cycloalkyl, preferably cyclohexyl,

5-6 membered heteroaryl, preferably isoxazolyl, pyrazolyl, thiazolyl, thiadiazolyl, thienyl, pyridyl, pyrimidinyl, and pyridazinyl, and

9-10 membered bicyclic and 13-14 membered tricyclic heterocyclyl, preferably 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, isoquinolyl, quinolyl, indolyl, isoindolyl, 2,3-dihydro-1H-indolyl, naphthyridinyl, quinozalinyl, benzo[d]isothiazolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, tetrahydroquinolinyl, indazolyl, 2,1,3-

benzothiadiazolyl, benzodioxanyl, benzothienyl, benzofuryl, benzimidazolyl, benzoxazolyl and benzthiazolyl;

wherein substituted R^1 is substituted with one or more substituents selected from halo, C_{1-6}-alkyl, optionally substituted C_{3-6}-cycloalkyl, optionally substituted phenyl, optionally substituted phenyl-C_1-C_4-alkylenyl, C_{1-2}-haloalkoxy, optionally substituted 4-6 membered heterocyclyl-C_1-C_4-alkyl, optionally substituted 4-6 membered heterocyclyl-C_2-C_4-alkenyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted phenyloxy, optionally substituted 4-6 membered heterocyclyloxy, optionally substituted 4-6 membered heterocyclyl-C_1-C_4-alkoxy, optionally substituted 4-6 membered heterocyclylsulfonyl, optionally substituted 4-6 membered heterocyclylamino, optionally substituted 4-6 membered heterocyclylcarbonyl, optionally substituted 5-6 membered heterocyclyl-C_{1-4}-alkylcarbonyl, C_{1-2}-haloalkyl, C_{1-4}-aminoalkyl, nitro, amino, hydroxy, oxo, cyano, aminosulfonyl, C_{1-2}-alkylsulfonyl, halosulfonyl, C_{1-4}-alkylcarbonyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkoxy, C_{1-3}-alkylamino-C_{1-3}-alkoxy-C_{1-3}-alkoxy, C_{1-4}-alkoxycarbonyl, C_{1-4}-alkoxycarbonylamino-C_{1-4}-alkyl, C_{1-4}-hydroxyalkyl,  and C_{1-4}-alkoxy, preferably bromo, chloro, fluoro, iodo, nitro, amino, cyano, aminoethyl, Boc-aminoethyl, hydroxy, oxo, aminosulfonyl, 4-methylpiperazinylsulfonyl, cyclohexyl, phenyl, phenylmethyl, morpholinylmethyl, 1-methylpiperazin-4-ylmethyl, 1-methylpiperazin-4-ylpropyl, morpholinylpropyl, piperidin-1-ylmethyl, 1-methylpiperidin-4-ylmethyl, 2-methyl-2-(1-methylpiperidin-4-yl)ethyl, morpholinylethyl, 1-(4-

morpholinyl)-2,2-dimethylpropyl, piperidin-4-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-1-ylethyl, 1-Boc-piperidin-4-ylethyl, piperidin-4-ylmethyl, 1-Boc-piperidin-4-ylmethyl, piperidin-4-ylpropyl, 1-Boc-piperidin-4-ylpropyl, piperidin-1-ylpropyl, pyrrolidin-1-ylpropyl, pyrrolidin-2-ylpropyl, 1-Boc-pyrrolidin-2-ylpropyl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, 1-Boc-pyrrolidin-2-ylmethyl, pyrrolidinylpropenyl, pyrrolidinylbutenyl, fluorosulfonyl, methylsulfonyl, methylcarbonyl, Boc, piperidin-1-ylmethylcarbonyl, 4-methylpiperazin-1-ylcarbonylethyl, methoxycarbonyl, aminomethylcarbonyl, dimethylaminomethylcarbonyl, 3-ethoxycarbonyl-2-methyl-fur-5-yl, 4-methylpiperazin-1-yl, 4-methyl-1-piperidyl, 1-Boc-4-piperidyl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-methyl-(1,2,3,6-tetrahydropyridyl), imidazolyl, morpholinyl, 4-trifluoromethyl-1-piperidinyl, hydroxybutyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, sec-butyl, trifluoromethyl, pentafluoroethyl, nonafluorobutyl, dimethylaminopropyl, 1,1-di(trifluoromethyl)-1-hydroxymethyl, 1,1-di(trifluoromethyl)-1-(piperidinylethoxy)methyl, 1,1-di(trifluoromethyl)-1-(methoxyethoxyethoxy)methyl, 1-hydroxyethyl, 2-hydroxyethyl, trifluoromethoxy, 1-aminoethyl, 2-aminoethyl, 1-(N-isopropylamino)ethyl, 2-(N-isopropylamino)ethyl, dimethylaminoethoxy, 4-chlorophenoxy, phenyloxy, azetidin-3-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, pyrrol-2-ylmethoxy, 1-Boc-pyrrol-2-ylmethoxy, pyrrol-1-ylmethoxy, 1-methyl-pyrrol-2-ylmethoxy, 1-isopropyl-pyrrol-2-ylmethoxy, 1-Boc-piperdin-4-ylmethoxy, piperdin-4-ylmethoxy, 1-methylpiperdin-4-yloxy, isopropoxy, methoxy and ethoxy;

wherein R^2 is one or more substituents independently selected from

H,
halo,
hydroxy,
amino,
C_{1-6}-alkyl,
C_{1-6}-haloalkyl,
C_{1-6}-alkoxy,
C_{1-2}-alkylamino,
aminosulfonyl,
C_{3-6}-cycloalkyl,
cyano,
C_{1-2}-hydroxyalkyl,
nitro,
C_{2-3}-alkenyl,
C_{2-3}-alkynyl,
C_{1-6}-haloalkoxy,
C_{1-6}-carboxyalkyl,
5-6-membered heterocyclyl-C_{1-6}-alkylamino,
unsubstituted or substituted phenyl and
unsubstituted or substituted 5-6 membered heterocyclyl,

preferably H, chloro, fluoro, bromo, amino, hydroxy, methyl, ethyl, propyl, oxo, dimethylamino, aminosulfonyl, cyclopropyl, cyano, hydroxymethyl, nitro, propenyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, carboxymethyl, morpholinylethylamino, propynyl, unsubstituted or substituted phenyl and unsubstituted or substituted heteroaryl selected from thienyl, fury, pyridyl, imidazolyl, and pyrazolyl;

wherein R^e and R^f are independently selected from H and C_{1-2}-haloalkyl,

preferably trifluoromethyl;

wherein R^7 is selected from H, C_{1-3}-alkyl, optionally substituted phenyl, optionally substituted phenyl-C_{1-3}-alkyl, optionally substituted 4-6 membered heterocyclyl, optionally substituted 4-6 membered heterocyclyl-C_1-C_3-alkyl, C_{1-3}-alkoxy-C_{1-2}-alkyl and C_{1-3}-alkoxy-C_{1-3}-alkoxy-C_{1-3}-alkyl; and

wherein R^{20} is one or more substituents selected from halo, amino, hydroxy, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkoxy, optionally substituted heterocyclyl-C_{1-6}-alkylamino, optionally substituted heterocyclyl-C_{1-6}-alkyl, C_{1-6}-alkylamino-C_{2-4}-alkynyl, C_{1-6}-alkylamino-C_{1-6}-alkoxy, C_{1-6}-alkylamino-C_{1-6}-alkoxy-C_{1-6}-alkoxy, and optionally substituted heterocyclyl-C_{2-4}-alkynyl,

preferably chloro, fluoro, amino, hydroxy, methyl, ethyl, propyl, trifluoromethyl, dimethylaminopropynyl, 1-methylpiperdinylmethoxy, dimethylaminoethoxyethoxy, methoxy and ethoxy;

and pharmaceutically acceptable isomers and derivatives thereof.

A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable derivatives thereof as follows:

N-(4-Isopropylphenyl) {2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3-(Isopropyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3-Isoquinolyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-Isopropylphenyl]{2-[(2-(3-pyridyl)ethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)phenyl]{2-[(2-(3-pyridyl)ethyl)amino](3-pyridyl)}carboxamide;

N-[4-(Methylpropyl)phenyl]{2-[(2-(3-pyridyl)ethyl)amino](3-pyridyl)}carboxamide;

{2-[(2-(3-Pyridyl)ethyl)amino](3-pyridyl)}-N-[3-(trifluoromethyl)phenyl]carboxamide;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-{4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl}carboxamide;

N-[5-(tert-Butyl)isoxazol-3-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[5-(tert-Butyl)-1-methylpyrazol-3-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)(1,3-thiazol-2-yl)]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[5-(tert-Butyl)(1,3,4-thiadiazol-2-yl)]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(4-Hydroxybutyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[2-(4-Chlorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino](3-pyridyl)carboxamide;

5-Bromo-N-[2-(4-chlorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino](3-pyridyl)carboxamide;

N-[2-(4-Phenoxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino](3-pyridyl)carboxamide;

N-[2-(4-Methoxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino](3-pyridyl)carboxamide;

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-Hydroxy-3-ethoxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-Fluorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino](3-pyridyl)carboxamide;

N-[2-(4-(tert-Butyl)phenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3-Fluorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3-Chlorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3-(Trifluoromethyl)phenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3-Ethoxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3,4-Dimethylphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(1,3-Benzodioxol-5-yl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-Methylphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-Hydroxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-Bromophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3,4-Dichlorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-(Fluorosulfonyl)phenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(3,5-(Dimethoxy)phenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(2,4-Dichlorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(2-Fluorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(2-Chlorophenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(4-(Aminosulphonyl)phenyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(2-Thienyl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(Pyridin-2-yl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)}carboxamide;

N-[2-(Pyridin-3-yl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-[2-(Pyridin-4-yl)ethyl]-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-(4-Phenylbutyl)-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

N-(2-Hydroxy-3-phenoxypropyl)-2-[(pyridin-4-ylmethyl)amino] (3-pyridyl)carboxamide;

{6-Chloro-5-fluoro-2-[(4-pyridylmethyl)amino](3-pyridyl)}-N-[4-(isopropyl)phenyl]carboxamide;

{5-Fluoro-2-[(4-pyridylmethyl)amino](3-pyridyl)}-N-[4-(isopropyl)phenyl]carboxamide;

2-[(Pyridin-4-ylmethyl)amino]-*N*-[4-*tert*-butyl-3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl](3-pyridyl)carboxamide;

N-(3,4-Dichlorophenyl){6-[(2-morpholin-4-ylethyl)amino]-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(Morpholin-4-ylmethyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-{2-[(tert-Butoxy)carbonylamino]ethyl}phenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(2-Aminoethyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)-3-nitrophenyl]{2-[(2-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3-Amino-4-(tert-butyl)phenyl]{2-[(2-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(Isopropyl)phenyl]{2-[(2-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3-Aminosulfonyl-4-chlorophenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-{3-[(4-Methylpiperazinyl)sulfonyl]phenyl}{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(1,1,2,2,2-Pentafluoroethyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(1,1,2,2,3,3,4,4,4-Nonafluorobutyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(Isopropyl)phenyl]{2-[(2-(1,2,4-triazolyl)ethyl)amino](3-pyridyl)}carboxamide;

(2-{[2-(2-Pyridylamino)ethyl]amino}(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide;

{2-[(1-(2-Pyridyl)pyrrolidin-3-yl)amino](3-pyridyl)}-N-[3-(trifluoromethyl)phenyl]carboxamide;

2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethyl-phenyl)-nicotinamide

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-(8-quinolyl)carboxamide hydrochloride;

N-[4-(4-Chlorophenoxy)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-(2,3,4-trifluorophenyl)carboxamide hydrochloride;

N-(2-Naphthyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(2-Phenoxyphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-(5,6,7,8-tetrahydronaphthyl) carboxamide hydrochloride;

N-(2H-Benzo[3,4-d]1,3-dioxolen-5-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-Naphthyl{2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide hydrochloride;

N-[3-Benzylphenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide hydrochloride;

N-(Cyclohexylethyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide hydrochloride;

N-(Cyclohexylethyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide hydrochloride;

N-Indan-2-yl{2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide hydrochloride;

N-[4-(tert-Butyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-sec-Butyl-phenyl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(4-Methylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-[4-trifluoromethoxy)phenyl] carboxamide;

N-(4-Ethylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-(4-Butylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-(4-Iodophenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-[3-(Hydroxyethyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3-Ethylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

Ethyl 2-methyl-5-[3-({2-[(4-pyridylmethyl)amino](3-pyridyl)}carbonylamino)phenyl]furan-3-carboxylate;

N-(3-Phenylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-Benzylphenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-(6-Ethyl(2-pyridyl)){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-(6-Propyl(2-pyridyl))(2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-[4-(tert-Butyl)(2-pyridyl)]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3-Hydroxyphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-[4-(Methylethyl)(2-pyridyl)]{2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide;

N-[3,5-bis(Trifluoromethyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-[4-Chloro-3-(trifluoromethyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)} carboxamide hydrochloride;

N-(3-Chlorophenyl){2-[(2-(4-pyridyl)ethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(4-Phenoxyphenyl){2-[(2-(2-pyridyl)ethyl)amino](3-pyridyl)}carboxamide;

2-[(Benzo[b]thiophen-3-ylmethyl)amino](3-pyridyl)}-N-(4-phenoxyphenyl)carboxamide;

N-(4-Phenoxyphenyl){2-[(2-(3-pyridyl)ethyl)amino](3-pyridyl)}carboxamide;

N-[4-(Methylsulfonyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(1-Acetylindolin-6-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-Indolin-6-yl{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-Indol-6-yl{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-Indol-5-yl{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-Indol-7-yl{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3-(tert-Butyl)pyrazol-5-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3-Phenylpyrazol-5-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-{2-[2-(dimethylamino)ethoxy]-5-(tert-butyl)phenyl}{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)-3-(4-methylpiperazinyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3-(4-Methylpiperazinyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(4-Methylpiperazinyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}formamide;

N-[1-(1-Methyl-(4-piperidyl))indolin-6-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[1-(1-Methyl-(4-piperidyl))indolin-6-yl]{2-[(2-(3-pyridyl)ethyl)amino](3-pyridyl)}carboxamide;

N-[1-(2-Piperidylethyl)indolin-6-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[1-(2-Piperidylacetyl)indolin-6-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3,3-Dimethyl-1-(1-methyl(4-piperidyl))indolin-6-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3,3-Dimethylindolin-6-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3-(1-Methyl-(4-piperidyl))indol-5-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(1,1-Dimethyl-3-morpholin-4-ylpropyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)phenyl]{2-[({2-[(1-methyl(4-piperidyl))-methoxy](4-pyridyl)}methyl)amino](3-pyridyl)}carboxamide;

N-(4-Bromo-2-fluorophenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)phenyl]{2-{[(2-chloro(4-pyridyl))methyl]amino}(3-pyridyl)}carboxamide;

{2-[({2-[3-(Dimethylamino)prop-1-ynyl](4-pyridyl)}methyl)amino](3-pyridyl)}-N-[4-(tert-butyl)phenyl]carboxamide;

{2-[[(2-Methoxy(4-pyridyl))methyl]amino}(3-pyridyl))-N-[4-(methylethyl)phenyl]carboxamide;

N-{3-[3-(Dimethylamino)propyl]-5-(trifluoromethyl)phenyl}-{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)-3-(3-piperid-1-ylpropyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)-3-(3-pyrrolidin-1-ylpropyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[3-((1E)-4-Pyrrolidin-1-ylbut-1-enyl)-4-(tert-butyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)-3-(3-morpholin-4-ylpropyl)phenyl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[1-(2-Morpholin-4-ylethyl)indol-6-yl]{2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)phenyl]{2-[(pyrimidin-4-ylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-Chlorophenyl){2-[(pyrimidin-4-ylmethyl)amino](3-pyridyl)}carboxamide;

{2-[(Pyrimidin-4-ylmethyl)amino](3-pyridyl)}-N-[3-(trifluoromethyl)phenyl]carboxamide;

N-[4-(Isopropyl)phenyl]{4-[(4-pyridylmethyl)amino]pyrimidin-5-yl}carboxamide;

{2-{[(2-{2-[2-(Dimethylamino)ethoxy]ethoxy}(4-pyridyl))methyl]amino}(3-pyridyl))-N-[4-(tert-butyl)phenyl]carboxamide;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-{4-[2,2,2-trifluoro-1-(2-piperidylethoxy)-1-(trifluoromethyl)ethyl]phenyl}carboxamide;

{2-{[(2-{2-[2-(Dimethylamino)ethoxy]ethoxy)(4-pyridyl))methyl]amino}-6-fluoro(3-pyridyl))-N-[3-(trifluoromethyl)phenyl]carboxamide;

N-[4-(*tert*-Butyl)phenyl]{6-fluoro-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

{6-Fluoro-2-[(4-pyridylmethyl)amino](3-pyridyl)}-N-[4-(isopropyl)phenyl]carboxamide;

{6-Fluoro-2-[(4-pyridylmethyl)amino](3-pyridyl)}-N-[3-(trifluoromethyl)phenyl]carboxamide;

N-(1-Bromo(3-isoquinolyl)){6-fluoro-2-[(4-pyridylmethyl)amino](3-pyridyl)}-carboxamide;

N-(4-Phenoxyphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(4-Phenylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(3-Phenoxyphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(4-Cyclohexylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(4-Imidazol-1-ylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-Morpholin-4-ylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(4-Cyanonaphthyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-[4-(trifluoromethyl)phenyl]carboxamide hydrochloride;

Methyl-4-({2-[(4-pyridylmethyl)amino]-3-pyridyl}carbonylamino)benzoate hydrochloride;

N-[4-(Isopropyl)phenyl]{2-[(4-quinolylmethyl)amino](3-pyridyl)}carboxamide;

N-[4-(tert-Butyl)phenyl]{2-[(6-quinolylmethyl)amino](3-pyridyl)}carboxamide;

{2-[(6-Quinolylmethyl)amino](3-pyridyl)}-N-[3-(trifluoromethyl)phenyl]carboxamide;

N-(4-chlorophenyl){3-[(4-pyridylmethyl)amino](2-thienyl)}carboxamide;

N-phenyl{3-[(4-pyridylmethyl)amino](2-thienyl)}carboxamide;

N-(4-chlorophenyl)-3-[(4-pyridinylmethylene)amino]-4-pyridinecarboxamide;

N-(4-chlorophenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3,4-dichlorophenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}-carboxamide;

N-(3-chlorophenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-chlorophenyl){3-[(4-pyridylmethyl)amino](2-pyridyl)}carboxamide;

N-(4-chlorophenyl){3-[(6-quinolylmethyl)amino](2-pyridyl)}carboxamide;

N-(3,4-dichlorophenyl){2-[(6-quinolylmethyl)amino](3-pyridyl)}-carboxamide;

N-(4-chlorophenyl){6-methyl-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3,4-dichlorophenyl){6-methyl-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3-fluoro-4-methylphenyl){6-methyl-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(3,4-dichlorophenyl){6-chloro-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-chlorophenyl){6-chloro-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

{6-chloro-2-[(4-pyridylmethyl)amino](3-pyridyl)}-N-(3-fluorophenyl)carboxamide;

N-(3-chlorophenyl){6-chloro-2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-chlorophenyl){3-[(4-pyridylmethyl)amino](4-pyridyl)}carboxamide;

N-(3-fluoro-4-methylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-chlorophenyl){2-[(4-quinolylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-chlorophenyl){2-[(5-quinolylmethyl)amino](3-pyridyl)}carboxamide;

N-(4-chlorophenyl){2-[(4-pyridylethyl)amino]-5-(3-thienyl)-(3-pyridyl)}carboxamide;

N-(4-chlorophenyl){5-(4-methoxyphenyl)-2-[(4-pyridylmethyl)amino]-(3-pyridyl)}carboxamide; and

N-(4-chlorophenyl){5-bromo-2-[(4-pyridylmethyl)amino]-(3-pyridyl)}carboxamide.

A family of specific compounds of particular interest within Formula II' consists of compounds and pharmaceutically-acceptable derivatives thereof as follows:

2-{[2-(1-Isopropyl-azetidin-3-ylmethoxy)-pyridin-4-ylmethyl]-amino}-N-(4-trifluoromethyl-phenyl)-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(1-isopropyl-azetidin-3-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-N-{4-[1-methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenyl}-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(2,3-dihydro-benzofuran-5-ylmethyl)-amino]-nicotinamide;

2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-N-[3,3-dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-nicotinamide;

2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-N-[3,3-dimethyl-1-(1-methylpiperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-({2-[2-(1-methyl-piperidin-4-yl)-ethoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

2-({2-[2-(1-Methyl-piperidin-4-yl)-ethoxy]-pyridin-4-ylmethyl)-amino)-N-(3-trifluoromethyl-phenyl)-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-ethylpyridin-4-ylmethyl]-amino}-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-({2-[2-(1-methyl-pyrrolidin-2-yl)-ethoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

2-({2-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-pyridin-4-ylmethyl)-amino)-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

N-(4-Pentafluoroethyl-phenyl)-2-{[2-(2-pyrrolidin-1-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(2-pyrrolidin-1-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-(4-Boc-piperazine-1-carbonyl)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-(4-Boc-piperazine-1-carbonyl)-5-trifluoromethyl-phenyl]-2-(2-pyridin-4-yl-ethylamino)-nicotinamide;

N-[3-(4-Methyl-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-(4-Boc-piperazin-1-ylmethyl)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-{[2-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-N-(4-trifluoromethyl-phenyl)-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(1-methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

2-({2-[3-(1-Methyl-piperidin-4-yl)-propoxy]-pyridin-4-ylmethyl}-amino)-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(1-Boc-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-yl)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[1-(2-Dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[1-(2-Dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(1-Boc-piperidin-4-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-[3,3-Dimethyl-1-(1-Boc-pyrrolidin-2-ylmethoxy)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3,3-Dimethyl-1-(2-Boc-amino-acetyl)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3,3-Dimethyl-1-(2-Boc-amino-acetyl)-2,3-dihydro-1H-indol-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(1-methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(1-Boc-piperidin-4-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(4-Boc-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide;

2-{[2-(3-Morpholin-4-yl-propoxy)-pyridin-4-ylmethyl]-amino}-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

(S) 2-{[2-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-4-ylmethyl]-amino)-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

N-(3-tert-Butyl-isoxazol-5-yl)-2-{[2-(3-morpholin-4-yl-propoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(3-morpholin-4-yl-propylamino)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(3-morpholin-4-yl-propoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(2-morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

2-{[2-(2-Morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-N-(4-trifluoromethyl-phenyl)-nicotinamide;

2-{[2-(2-Morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-N-(3-trifluoromethyl-phenyl)-nicotinamide;

2-{[2-(2-Morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

N-(3-tert-Butyl-isoxazol-5-yl)-2-{[2-(2-morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(2-morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(1-methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

2-{[2-(1-Methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-N-(4-trifluoromethyl-phenyl)-nicotinamide;

2-{[2-(1-Methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

2-{[2-(1-Methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-N-(4-tert-butyl-phenyl)-nicotinamide;

(R) N-(4-tert-Butyl-phenyl)-2-{[2-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

(R) N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

(R) N-[3-(1-Methyl-pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-(1-Methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-(1-Methyl-piperidin-4-ylmethyl)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-tert-Butyl-4-(1-Boc-pyrrolidin-2-ylmethoxy)-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(3,3-Dimethyl-2,3-dihydro-benzofuran-6-yl)-2-{[2-(1-methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

2-({2-[3-(1-Methyl-piperidin-4-yl)-propoxy]-pyridin-4-ylmethyl}-amino)-N-(4-trifluoromethyl-phenyl)-nicotinamide;

2-({2-[3-(1-Methyl-piperidin-4-yl)-propoxy]-pyridin-4-ylmethyl}-amino)-N-(3-trifluoromethyl-phenyl)-nicotinamide;

2-({2-[3-(1-Methyl-piperidin-4-yl)-propoxy]-pyridin-4-ylmethyl}-amino)-N-(4-tert-butyl-phenyl)-nicotinamide;

2-({2-[3-(1-Methyl-piperidin-4-yl)-propoxy]-pyridin-4-ylmethyl}-amino)-N-(3-tert-butyl-isoxazol-5-yl)-nicotinamide;

N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-({2-[3-(1-methyl-piperidin-4-yl)-propoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

2-[(Pyridin-4-ylmethyl)-amino]-N-(3,9,9-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluoren-6-yl)-nicotinamide;

N-[3,3-Dimethyl-1-(1-Boc-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(4-Imidazol-1-ylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-[3,3-Dimethyl-1-(1-methyl-piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-{[2-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

N-(3-tert-Butyl-isoxazol-5-yl)-2-{[2-(1-methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(1-methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-ylmethyl]-amino}-nicotinamide;

2-{[2-(3-Morpholin-4-yl-propylamino)-pyrimidin-4-ylmethyl]-amino)-N-(4-pentafluoroethyl-phenyl)-nicotinamide;

2-{[2-(3-Morpholin-4-yl-propylamino)-pyrimidin-4-ylmethyl]-amino}-N-(3-trifluoromethyl-phenyl)-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-({2-[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-pyrimidin-4-ylmethyl}-amino)-nicotinamide;

N-(1-Acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-({2-[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-pyrimidin-4-ylmethyl}-amino)-nicotinamide;

N-(4-Phenoxyphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

2-{[2-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-N-[3-(1-methyl-piperidin-4-yl)-5-trifluoromethyl-phenyl]-nicotinamide;

N-(3-tert-Butyl-isoxazol-5-yl)-2-{[2-(1-methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-[3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(1-Boc-azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-(3,3-Dimethylindolin-6-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide phosphate salt;

N-(4-Morpholin-4-ylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(4-Cyanonaphthyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide, hydrochloride;

{2-[(4-Pyridylmethyl)amino](3-pyridyl)}-N-[4-(trifluoromethyl)phenyl]carboxamide hydrochloride;

Methyl-({2-[(4-pyridylmethyl)amino]-3-pyridyl}carbonylamino)benzoate, hydrochloride;

2-[(Pyridin-4-ylmethyl)-amino]-N-(2,2,4-trimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-nicotinamide;

N-(4-Acetyl-2,2-dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(2,2-Dimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-{[2-(1-Benzhydryl-azetidin-3-yloxy)-pyridin-4-ylmethyl]-amino}-N-(4-tert-butyl-phenyl)-nicotinamide;

N-(4,4-Dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-({2-[2-(1-methyl-piperidin-4-yl)-ethoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

N-(3-tert-Butyl-isoxazol-5-yl)-2-({2-[2-(1-methyl-piperidin-4-yl)-ethoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

N-(3-trifluoromethylphenyl)-2-({2-[2-(1-methyl-piperidin-4-yl)-ethoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

2-[(2,3-Dihydro-benzofuran-6-ylmethyl)-amino]-N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-nicotinamide;

N-[3-(1-Methyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide hydrochloride;

(R) N-[3-(2-Hydroxy-3-pyrrolidin-1-yl-propoxy)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

(S) N-[3-(2-Hydroxy-3-pyrrolidin-1-yl-propoxy)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[4-tert-Butyl-3-(1-methyl-piperidin-4-ylmethoxy)-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3-(1-Methyl-piperidin-4-ylmethoxy)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[4-Pentafluoroethyl-3-(2-piperidin-1-yl-ethoxy)-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethyl-phenyl)-nicotinamide hydrochloride;

N-(4-Imidazol-1-ylphenyl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(3,3-Dimethyl-2,3-dihydro-benzofuran-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide hydrochloride;

2-[(Pyridin-4-ylmethyl)-amino]-N-(4-tert-butyl-phenyl)-nicotinamide hydrochloride;

N-[4-Trifluoromethyl-3-(2-piperidin-1-yl-ethoxy)-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

(S) N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

(R) N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

(R) N-[3-(1-Boc-pyrrolidin-2-ylmethoxy)-4-pentafluoroethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(4-tert-Butyl-phenyl)-2-{[2-(1-methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(3-Trifluoromethyl-phenyl)-2-{[2-(1-methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(3-tert-Butyl-isoxazol-5-yl)-2-{[2-(1-methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-[3-(3-Piperidin-1-yl-propyl)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide ;

N-[3-(3-Morpholin-4-yl-propyl)-5-trifluoromethyl-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(1-Boc-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-(3,3-Dimethylindolin-6-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide edisylate;

N-{4-tert-Butyl-3-[2-(1-Boc-piperidin-4-yl)-ethyl]-phenyl}-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide ;

N-[4-tert-Butyl-3-(1-methyl-azetidin-3-ylmethoxy)-phenyl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(3,3-Dimethyl-1,1-dioxo-2,3-dihydro-1H-1λ-benzo[d]isothiazol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[1,1,4,4-Tetramethyl-1,2,3,4-tetrahydro-naphth-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-{4-[1-Methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenyl}-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-(4-[1-methyl-1-(1-methyl-piperidin-4-yl)-ethyl]-phenyl}-nicotinamide;

N-(3,3-Dimethyl-2,3-dihydro-benzofuran-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-({2-[2-(1-methyl-piperidin-4-yl)-ethoxy]-pyridin-4-ylmethyl}-amino)-nicotinamide;

2-[(Pyridin-4-ylmethyl)-amino]-N-[3-(2-pyrrolidin-1-yl-ethoxy)-4-trifluoromethyl-phenyl]-nicotinamide hydrochloride;

N-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(4,4-Dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(3,3-Dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(1-methyl-piperidin-4-ylmethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(3,3-Dimethylindolin-6-yl){2-[(4-pyridylmethyl)amino](3-pyridyl)}carboxamide hydrochloride;

N-(3,3-Dimethyl-1-piperidin-4-yl-2,3-dihydro-1H-indol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-({2-[2-(1-methyl-pyrrolidin-2-yl)-ethylamino]-pyrimidin-4-ylmethyl}-amino)-nicotinamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-[3,3-Dimethyl-1-(piperidin-4-ylmethyl)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

N-(3,3-Dimethyl-1-piperidin-4-yl-2,3-dihydro-1H-indol-6-yl)-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(piperidin-4-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-[3,3-Dimethyl-1-(pyrrolidin-2-ylmethoxy)-2,3-dihydro-1H-indol-6-yl]-2-[(2-methoxy-pyridin-4-ylmethyl)-amino]-nicotinamide;

2-[(2-Methoxy-pyridin-4-ylmethyl)-amino]-N-[3-(piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-nicotinamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(2-morpholin-4-yl-ethoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(2-morpholin-4-yl-propylamino)-pyridin-4-ylmethyl]-amino}-nicotinamide hydrochloride;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(1-methyl-piperidin-4-yloxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-{[2-(2-morpholin-4-yl-propoxy)-pyridin-4-ylmethyl]-amino}-nicotinamide;

N-(4-Pentafluoroethyl-phenyl)-2-[(pyrimidin-4-ylmethyl)-amino]-nicotinamide;

2-{[2-(Azetidin-3-yloxy)-pyridin-4-ylmethyl]-amino}-N-(4-tert-butyl-phenyl)nicotinamide;

N-(2,3,3-Trimethyl-1,1-dioxo-2,3-dihydro-1H-1λ-benzo[d]isothiazol-6-yl)-2-[(pyridin-4-ylmethyl)-amino]-benzamide;

N-(4,4-Dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide hydrochloride;

N-[3,3-Dimethyl-1,1-dioxo-2-(2-piperidin-1-yl-ethyl)-2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide; and

N-[2-(2-Dimethylamino-ethyl)-3,3-dimethyl-1,1-dioxo-2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl]-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide.

Indications

Compounds of the present invention would be useful for, but not limited to, the prevention or treatment of angiogenesis related diseases. The compounds of the

invention have kinase inhibitory activity, such as VEGFR/KDR inhibitory activity. The compounds of the invention are useful in therapy as antineoplasia agents or to minimize deleterious effects of VEGF.

Compounds of the invention would be useful for the treatment of neoplasia including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

Preferably, the compounds are useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

The compounds also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage;

ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

The compounds of the invention are useful in therapy of proliferative diseases. These compounds can be used for the treatment of an inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermato-myositis, systemic sclerodermia or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof. An example of an inflammation related disorder is (a) synovial inflammation, for example, synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial inflammation may for example, be consequential to or associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans. The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the region of the tendon insertions and tendon sheaths. Such

inflammation may be, for example, consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy, myofasciale syndrome and tendomyosis. The present invention is further especially applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

These compounds can be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein- Leventhal syndrome)) since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in treating disorders in which protein extravasation leads to

the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome).

The compounds of the present invention are also useful in the treatment of ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis.

The compounds of the present invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anaemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease. The compounds are also useful in the reduction of sub-cutaneous fat and for the treatment of obesity.

The compounds of the present invention are also useful in the treatment of ocular conditions such as ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, glaucoma, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and

osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukemia and lymphoma, tumor- induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy.

The compounds of this invention may also act as inhibitors of other protein kinases, e.g. p38, EGFR, CDK-2, CDK-5, IKK, JNK3, and thus be effective in the treatment of diseases associated with other protein kinases.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

As used herein, the compounds of the present invention include the pharmaceutically acceptable derivatives thereof.

Definitions

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a preclinically evident stage of disorders in individuals).

The term "prevention" includes either preventing the onset of disorders altogether or delaying the onset of a preclinically evident stage of disorders in individuals. This includes prophylactic treatment of those at risk of developing a disease, such as a cancer, for example. "Prophylaxis" is another term for prevention.

A "pharmaceutically-acceptable derivative " denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly-proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl. The term "lower alkyl substituted with R^2" does not include an acetal moiety.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about

six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 to 3 substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino. Phenyl substituted with $-O-CH_2-O-$ forms the aryl benzodioxolyl substituent.

The term " heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring

radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-,-O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl

[e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. Other preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur, nitrogen and oxygen, selected from thienyl, furyl, pyrrolyl, indazolyl, pyrazolyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

Particular examples of non-nitrogen containing heteroaryl include pyranyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzofuryl, benzothienyl, and the like.

Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl,

morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals,

respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The term "heterocyclylalkylenyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkylenyl radicals are "5- or 6-membered heteroarylalkylenyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH_3S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower

haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are substituted with one alkyl radical and with two independent alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C_1-C_3-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl"

radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH_2 groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C_1-C_3-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are

"lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C_3-C_6 rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C_3-C_6 rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

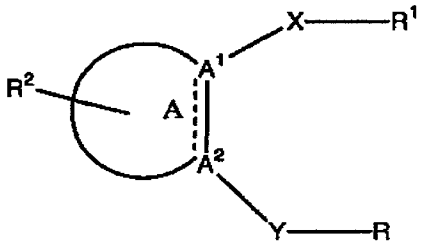
The phrase "Formula I-XII" includes sub formulas such as II'.

The compounds of the invention are endowed with kinase inhibitory activity, such as KDR inhibitory activity.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of KDR.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas I-XII in association with a least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically-effective amount of a compound of Formula I



I

wherein each of A^1 and A^2 is independently C, CH or N;

wherein ring A is selected from

a) 5- or 6-membered partially saturated heterocyclyl,

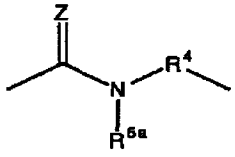
b) 5- or 6-membered heteroaryl,

c) 9-, 10- or 11-membered fused partially saturated heterocyclyl,

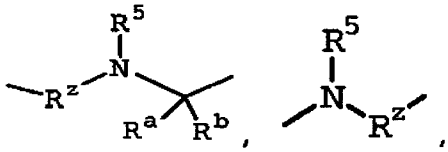
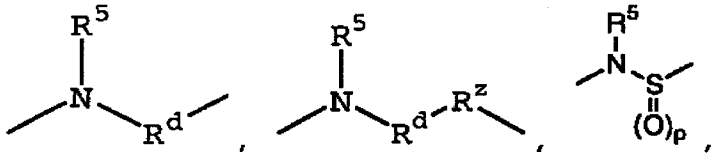
d) 9-, 10- or 11-membered fused heteroaryl;

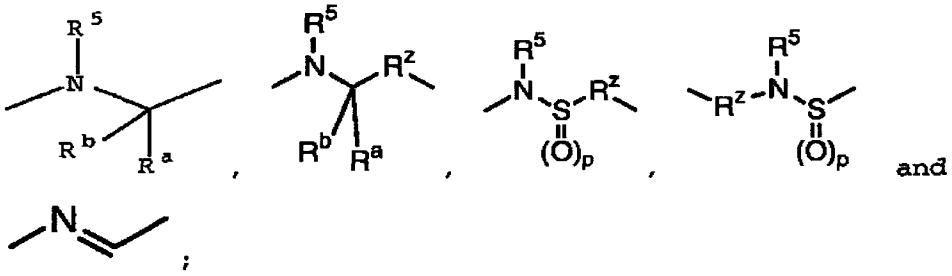
e) naphthyl, and

f) 4-, 5- or 6- membered cycloalkenyl;

wherein X is  ;

wherein Z is oxygen or sulfur;

wherein Y is selected from  ,  ,



wherein p is 0 to 2,

wherein R^a and R^b are independently selected from H, halo, cyano, $-NHR^6$ and C_{1-4}-alkyl substituted with R^2, or wherein R^a and R^b together form C_3-C_6 cycloalkyl;

wherein R^z is selected from C_2-C_6-alkylenyl, where one of the CH_2 groups may be replaced with an oxygen atom or an -NH-; wherein one of the CH_2 groups may be substituted with one or two radicals selected from halo, cyano, $-NHR^6$ and C_{1-4}-alkyl substituted with R^2;

wherein R^d is cycloalkyl;

wherein R is selected from

a) substituted or unsubstituted 5-6 membered heterocyclyl, b) substituted aryl, and

c) substituted or unsubstituted fused 9-14-membered bicyclic or tricyclic heterocyclyl;

wherein substituted R is substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-SO_2R^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, nitro, alkylaminoalkoxyalkoxy, cyano, alkylaminoalkoxy, lower alkyl substituted with R^2, lower alkenyl substituted with R^2, and lower alkynyl substituted with R^2;

wherein R^1 is selected from

a) substituted or unsubstituted 6-10 membered aryl,

b) substituted or unsubstituted 5-6 membered heterocyclyl,

c) substituted or unsubstituted 9-14 membered bicyclic or tricyclic heterocyclyl,

d) cycloalkyl, and

e) cycloalkenyl,

wherein substituted R^1 is substituted with one or more substituents independently selected from halo, $-OR^3$, $-SR^3$, $-CO_2R^3$, $-CONR^3R^3$, $-COR^3$, $-NR^3R^3$, $-NH(C_1-C_4$ alkylenyl$R^{14})$, $-SO_2R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, optionally substituted cycloalkyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted phenyl, halosulfonyl, cyano, alkylaminoalkoxy, alkylaminoalkoxyalkoxy, nitro, lower alkyl substituted with R^2, lower alkenyl substituted with R^2, and lower alkynyl substituted with R^2;

wherein R^2 is one or more substituents independently selected from H, halo, $-OR^3$, oxo, $-SR^3$, $-CO_2R^3$, $-COR^3$, $-CONR^3R^3$, $-NR^3R^3$, $-SO_2NR^3R^3$, $-NR^3C(O)OR^3$, $-NR^3C(O)R^3$, cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl, lower carboxyalkyl, nitro, lower alkenyl, lower alkynyl, lower aminoalkyl, lower alkylaminoalkyl and lower haloalkyl;

wherein R^3 is selected from H, lower alkyl, phenyl, heterocyclyl, C_3-C_6-cycloalkyl, phenylalkyl, heterocyclylalkyl, C_3-C_6 cycloalkylalkyl, and lower haloalkyl;

wherein R^4 is selected from a direct bond, C_{2-4}-alkylenyl, C_{2-4}-alkenylenyl and C_{2-4}-alkynylenyl, where one of the CH_2 groups may be substituted with an oxygen atom or an -NH-, wherein R^4 is optionally substituted with hydroxy;

wherein R^5 is selected from H, lower alkyl, phenyl and lower aralkyl;

wherein R^{5a} is selected from H, lower alkyl, phenyl and lower aralkyl;

wherein R^{6} is selected from H or C_{1-6}-alkyl; and

wherein R^{14} is selected from H, phenyl, 5-6 membered heterocyclyl and C_3-C_6 cycloalkyl;

and pharmaceutically acceptable derivatives thereof; provided A is not naphthyl when X is -C(O)NH- and when R^1 is phenyl when Y is $-NCH_2-$ and when R is 4-pyridyl; and further provided R is not unsubstituted 2-thienyl, 2-pyridyl or 3-pyridyl when Y is $-NHCH_2-$.

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the

prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with, or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited

to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents which may be used in combination with compounds of the present invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22,

spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine,

tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α-carotene, α-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110,

American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanlne derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER,

ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon

alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic

acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as other kinase inhibitors including p38 inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, NSAID's, SOD mimics or $\alpha_v\beta_3$ inhibitors.

The present invention comprises processes for the preparation of a compound of Formula I-XII.

Also included in the family of compounds of Formula I-XII are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I-XII may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric,

pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I-XII include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, aistidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formula I-XII.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

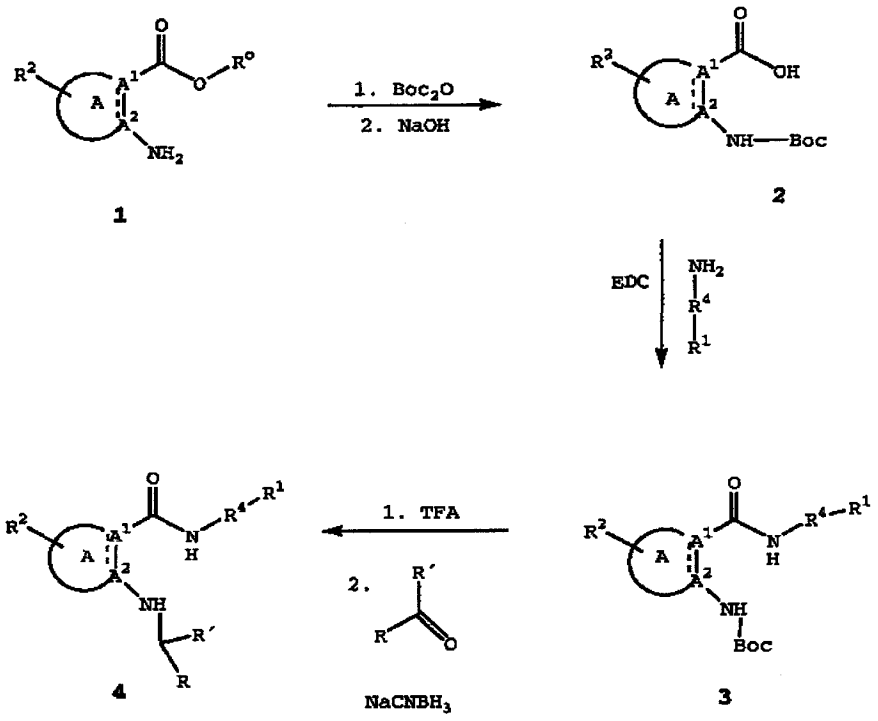
Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases. Preferred salts include hydrochloride, phosphate and edisylate.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66, 1 (1977).

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes 1-48, wherein the substituents are as defined for Formulas I-XII, above, except where further noted.

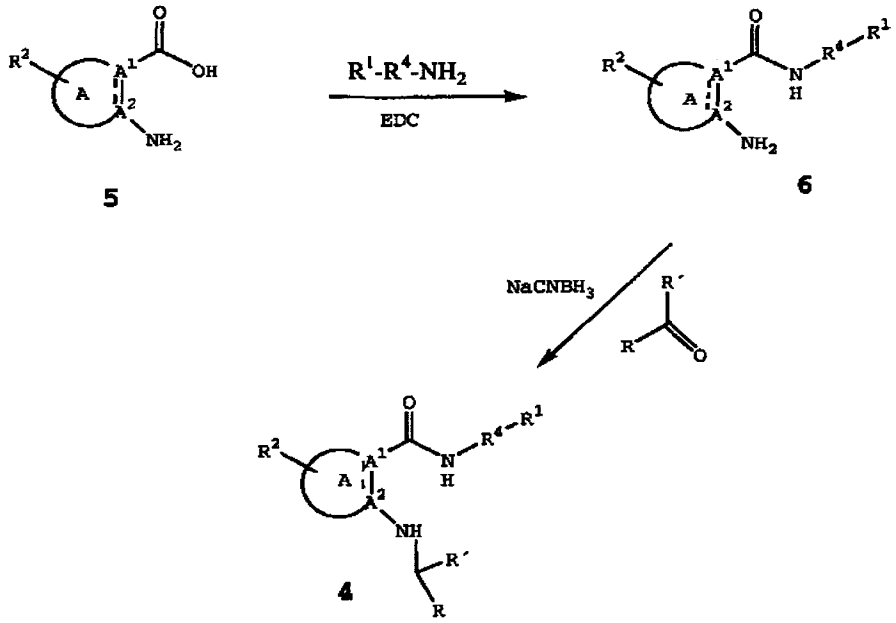
Scheme 1



Cyclic amides can be prepared according to the method set out in Scheme 1. The amino group of compound **1** (where R^{o} is alkyl, aryl, and the like) is protected, such as with Boc anhydride, followed by treatment, to remove the ester, such as with base, forming the protected amine/free acid **2**. Alternatively, other amino protecting groups known in the art can be used. Substituted amines are coupled with the free acid, such as with EDC, to form the protected amine/amide **3**. The protected amine moiety is deprotected, such as with acid, and reacted via one step reductive alkylation with carbonyl-containing compounds (where R′ is H, halo, cyano, $-NHR^{6}$ and C_{1-4} alkyl) to form the 1-amido-2-substituted amino-compounds **4**. Preferably the amination is in an alcohol, such as MeOH, EtOH or propanol, and at a temperature between about 0-50°C, such as RT. Aldehydes or

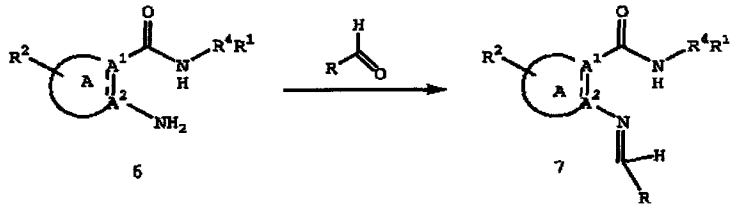
ketones are preferred carbonyl-containing compounds. Alternative carbonyl-containing compounds are, for example, bisulfite adducts or hemiacetals, acetals, hemiketals or ketals of compounds with alcohols, for example lower hydroxyalkyl compounds; or thioacetals or thioketals of compounds with mercaptans, for example lower alkylthio compounds. The reductive alkylation is preferably carried out with hydrogenation in the presence of a catalyst, such as platinum or especially palladium, which is preferably bonded to a carrier material, such as carbon, or a heavy metal catalyst, such as Raney nickel, at normal pressure or at pressures of from 0.1 to 10 MegaPascal (MPa), or with reduction by means of complex hydrides, such as borohydrides, especially alkali metal cyanoborohydrides, for example sodium cyanoborohydride, in the presence of a suitable acid, preferably relatively weak acids, such as lower alkylcarboxylic acids, especially acetic acid, or a sulfonic acid, such as p-toluenesulfonic acid; in customary solvents, for example alcohols, such as MeOH or EtOH, or ethers, for example cyclic ethers, such as THF, in the presence or absence of water.

Scheme 2



Alternatively, compounds **4** can be prepared from mixed acid/amines **5** as shown in Scheme 2. Substituted amines are coupled with the mixed acid/amines **5** such as with a coupling reagent, for example EDC, to form the mixed amine/amide **6**. Substituted carbonyl compounds, such as acid halides, anhydrides, carboxylic acids, esters, ketones, aldehydes and the like, are added to the mixed amine/amide **6** followed with reduction to give the substituted amide/substituted amine compounds **4**.

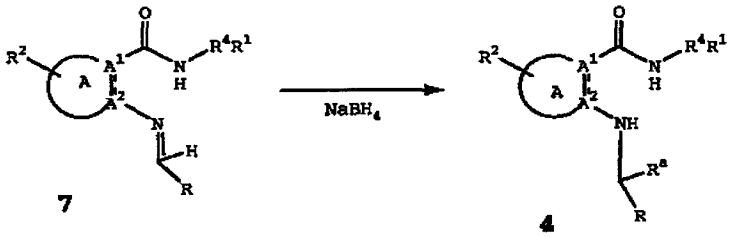
Scheme 3



6 7

Imino compounds **7** can be formed from the mixed amine/amides **6**, such as by reacting with a substituted carbonyl compound.

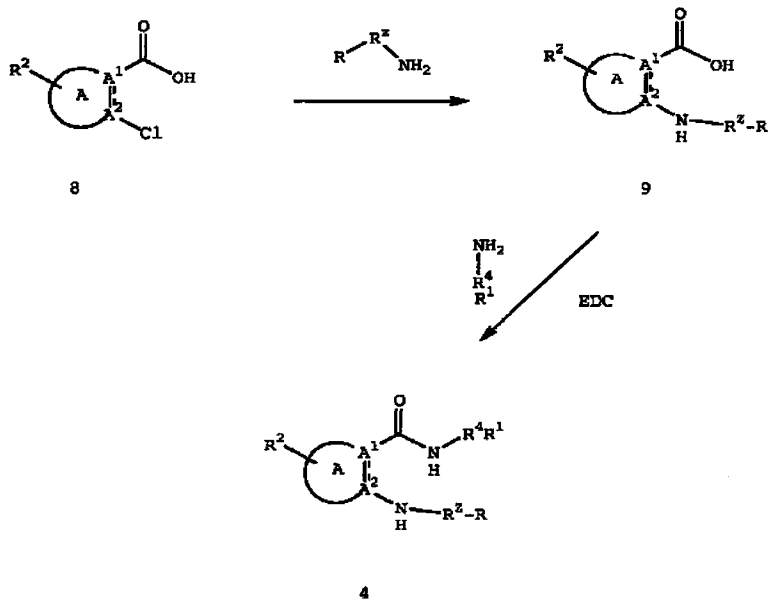
Scheme 4



7 4

Substituted cyclic carboxamides can be prepared from the corresponding imino analogs by the process outlined in Scheme 4. Treatment of the imino compound **7** with a reducing agent yields compound **4**. Reagents which can be used to add hydrogen to an imine double bond include borane in THF, $LiAlH_4$, $NaBH_4$, sodium in EtOH and hydrogen in the presence of a catalyst, and others.

Scheme 5



Substituted carboxamides **4** can be prepared from the corresponding halo analogs **8** by the process outlined in Scheme 5. Substituted amino acids **9** are prepared from the corresponding chloro compounds **8** such as by reacting with an amine at a suitable temperature, such as about 80°C. The acid **9** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding amide **4**.

The amination process can be carried out as an Ullmann type reaction using a copper catalyst, such as copper[0] or a copper[I] compound such as copper[I]oxide, copper[I]bromide or copper[I]iodide in the presence of a suitable base (such as a metal carbonate, for example K_2CO_3) to neutralize the acid generated in the reaction. This reaction is reviewed in Houben-Weyl "Methoden der Organischen Chemie", Band 11/1, page 32 -33, 1958, in Organic Reactions, 14, page 19-24, 1965 and by J. Lindley

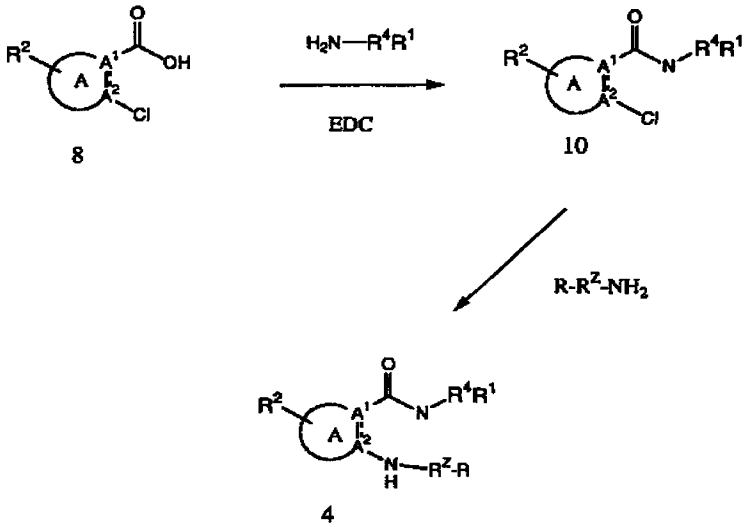
(1984) in Tetrahedron, 40, page 1433-1456. The amount of catalyst is typically in the range of 1 to 20 mole percent. The reaction is carried out in an inert, aprotic solvent such as an ether (for example dimethoxyethane or dioxane) or an amide (for example dimethylformamide or *N*-methylpyrrolidone), under an inert atmosphere in the temperature range of 60-180°C.

An alternative amination process involves using a Group VIII element, where the metal core of the catalyst should be a zero-valent transition metal, such as palladium or nickel, which has the ability to undergo oxidative addition to the aryl-halogen bond. The zero valent state of the metal may be generated in situ from the M[II] state. The catalyst complexes may include chelating ligands, such as alkyl, aryl or heteroaryl derivatives of phosphines or biphosphines, imines or arsines. Preferred catalysts contain palladium or nickel. Examples of such catalysts include palladium[II]chloride, palladium[II]acetate, tetrakis(triphenyl-phosphine)palladium[0] and nickel[II]acetylacetonate. The metal catalyst is typically in the range of 0.1 to 10 mole percent. The chelating ligands may be either monodentate, as in the case for example of trialkyphosphines, such as tributylphosphine, triarylphosphines, such as tri-(*ortho*-tolyl)phosphine, and triheteroaryl phosphines, such as tri-2-furylphosphine; or they may be bidentate such as in the case of 2,2'-bis(diphenylphosphino)- 1,1'binaphthyl, 1,2-bis(diphenylphosphino)ethane, 1,1'-bis(diphenylphosphino)ferrocene and 1-(*N*,*N*-dimethyl-amino)-1'-(dicyclohexylphosphino)biphenyl. The supporting ligand may be complexed to the metal center in the form of a metal complex prior to being added to the reaction mixture or may be added to the reaction mixture as a separate compound. The supporting ligand is typically present in the range 0.01 to

20 mole percent. It is often necessary to add a suitable base to the reaction mixture, such as a trialkylamine (for example DIEA or 1,5-diazabicyclo[5,4,0]undec-5-ene), a Group I alkali metal alkoxide (for example potassium *tert*-butoxide) or carbonate (for example cesium carbonate) or potassium phosphate. The reaction is typically carried out in an inert aprotic solvent such as an ether (for example dimethoxyethane or dioxane) or an amide (for example, DMF or *N*-methylpyrrolidone), under an inert atmosphere in the temperature range of 60-180°C.

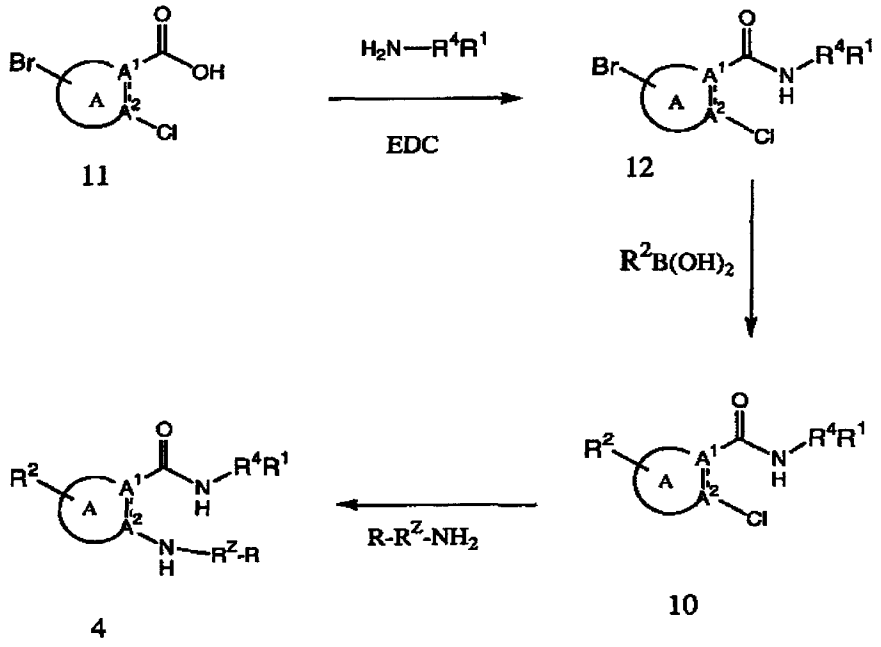
The amination is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example DMF or dimethylacetamide, a cyclic ether, for example THF or dioxane, or a nitrile, for example CH_3CN, or in a mixture thereof, at an appropriate temperature, for example in a temperature range of from about 40°C to about 180°C, and if necessary under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

Scheme 6



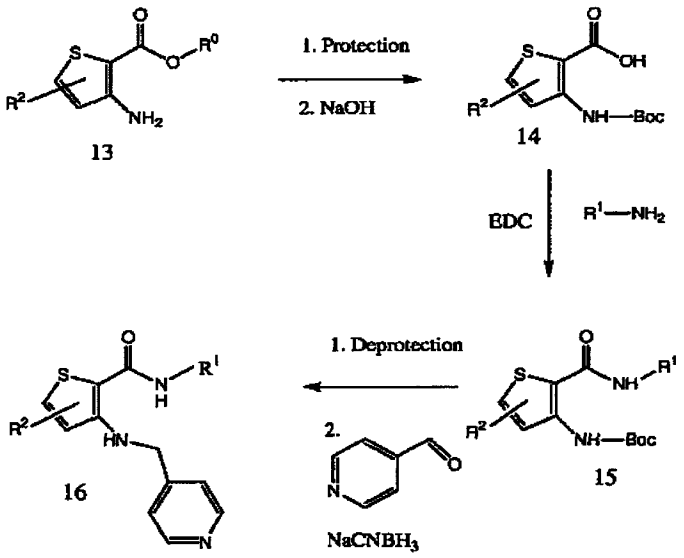
Substituted carboxamides **4** can be prepared from the corresponding halo analogs **8** by the process outlined in Scheme 6. The chloro acid **8** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding chloro amide **10**. Substituted amino-amides **4** are prepared from the corresponding chloro compounds **10** such as by reacting with an amine at a suitable temperature, such as about 80°C. The amination reaction can be run in the presence of an appropriate catalyst such as a palladium catalyst, in the presence of an aprotic base such as sodium *t*-butoxide or cesium carbonate, or a nickel catalyst, or a copper catalyst.

Scheme 7



Substituted carboxamides **4** can be prepared from the corresponding bromo/chloro analogs **11** by the process outlined in Scheme 7. The bromo/chloro acid **11** is coupled with an amine, preferably in the presence of a coupling agent such as EDC, to form the corresponding bromo substituted amide **12**. Suzuki coupling with the bromo amide **12** and suitable boronic acids provides the substituted amide **10**. Substituted amino-amides **4** are prepared from the corresponding chloro compounds **10** as described in Scheme 6.

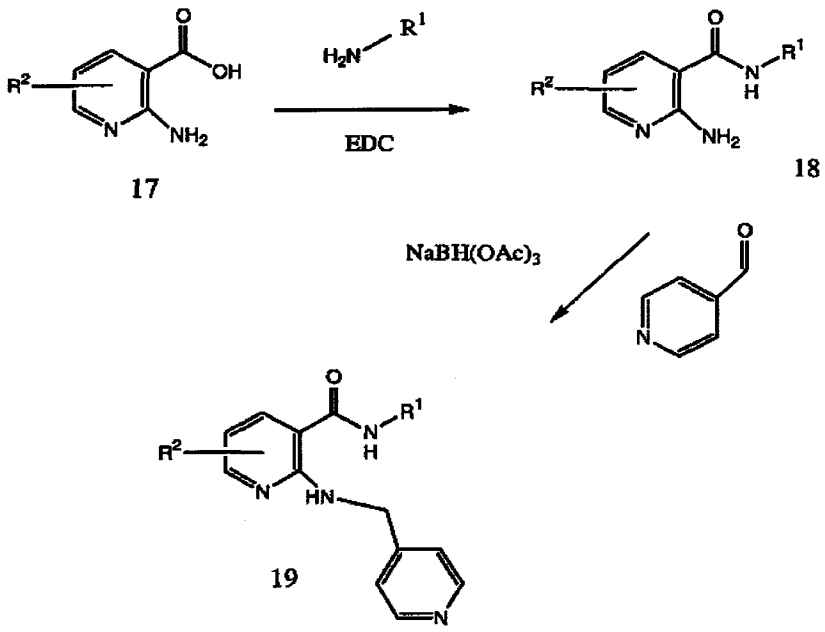
Scheme 8



Substituted thiophenes **16** can be prepared by the method of Scheme 8. The free amino group of a 3-amino-2-thiophenecarboxylic acid ester **13** can be protected such as by the addition of Boc_2O in a suitable solvent such as CH_2Cl_2 and DMAP. The ester is removed such as with base to form the free acid **14**. The thiophene amide **15** is formed from the acid **14** such as by coupling with a substituted amine in the presence of DIEA, EDC and HOBt. The 2-protected-amino-

thiophene amide **15** is deprotected, such as with 25% TFA/CH_2Cl_2. The free amine is alkylated such as with a substituted carboxaldehyde or similar active carbonyl compound, in the presence of a reducing agent $NaCNBH_3$ and the like, to form compounds **16**.

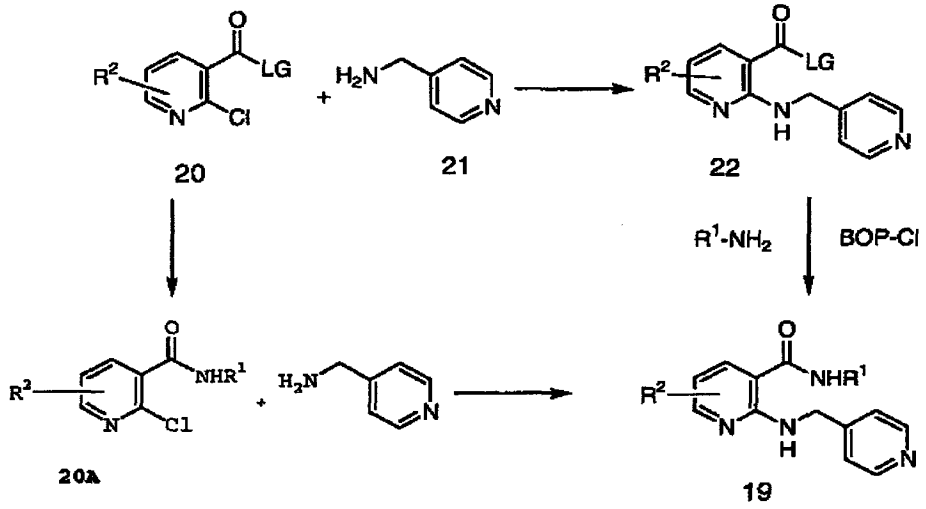
Scheme 9



17 18 19

Substituted pyridines can be prepared such as by the method found in Scheme 9. 2-Aminonicotinic acid **17** is coupled with a substituted amine at a suitable temperature, nonprotic solvent such as CH_2Cl_2, such as with EDC and HOBt, to form the nicotinamide **18**. The nicotinamide **18** is reductively alkylated such as with 4-pyridinecarboxaldehyde and $NaBH(OAc)_3$, to yield the 2-substituted amino-pyridyl carboxamides **19**.

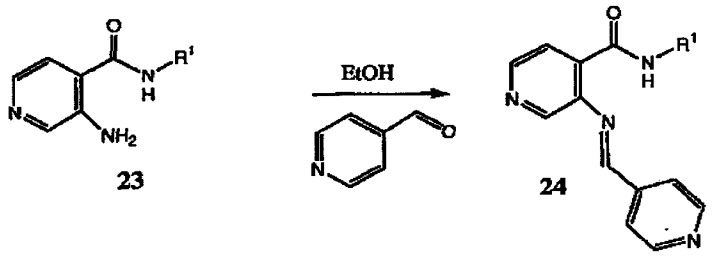
Scheme 10



Substituted pyridines may be prepared by the method found in Scheme 10. 2-Chloro-nicotinic acid **20** is coupled with an amine **21** at a suitable temperature, such as a temperature over about 100°C to give the 2-substituted amino-nicotinic acid **22**. The 2-substituted amino-nicotinic acid **22** is reacted with a substituted amine in the presence of a coupling reagent, such as BOP-Cl and base, such as TEA to form the 2-substituted amino-nicotinamide **19**.

Alternatively, 2-chloro-nicotinoyl chloride (LG is Cl) is coupled first with R^1-NH_2 such as in the presence of base, e.g., $NaHCO_3$, in a suitable solvent, such as CH_2Cl_2, to form the amide **20A**, then coupling with a pyridylmethylamine to yield the 2-substituted amino-nicotinamide **19**.

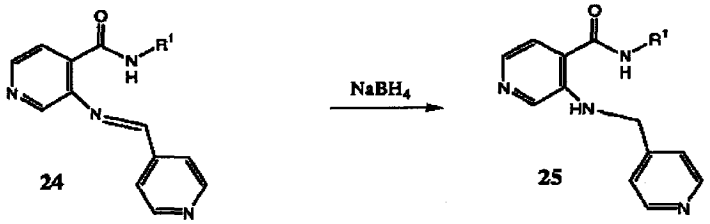
Scheme 11



23 24

Imino-substituted pyridines may be prepared by the method found in Scheme 11. (2-Amino-(4-pyridyl))-carboxamide **23** is reacted with 4-pyridine-carboxaldehyde, such as in the presence of p-toluenesulfonic acid monohydrate to yield the imino compound **24**.

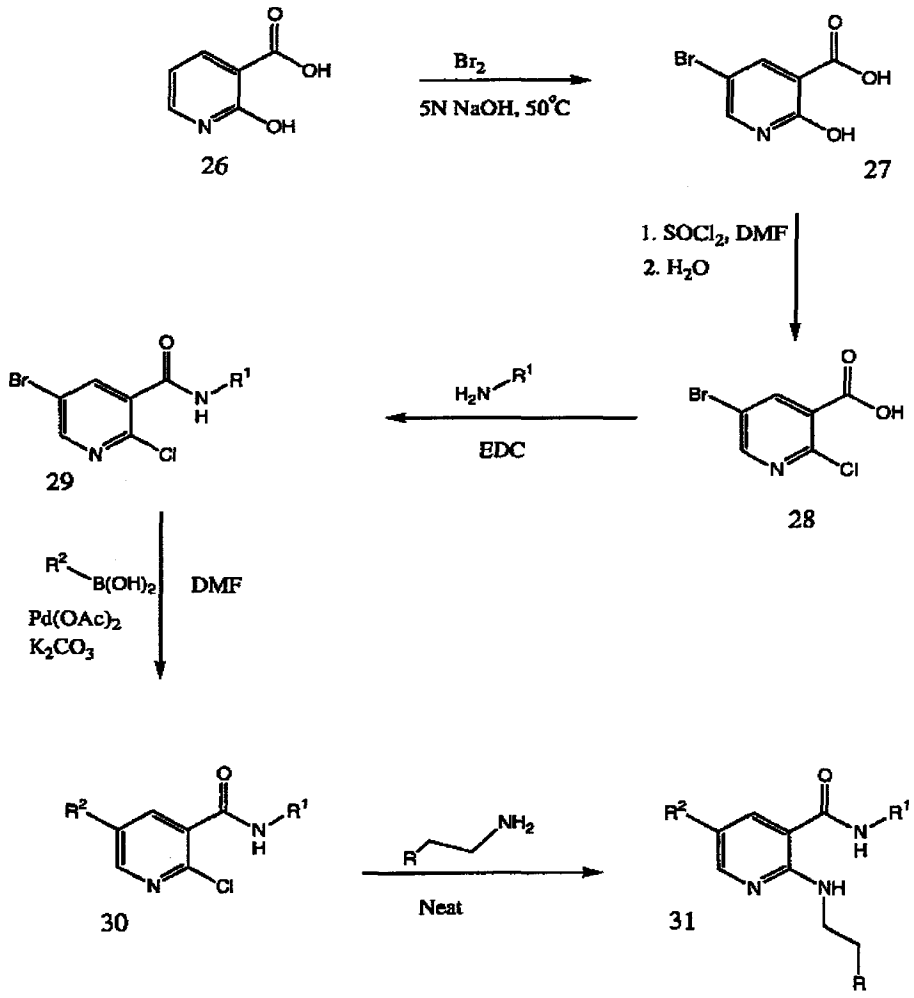
Scheme 12



24 25

Substituted pyridines alternatively may be prepared by the method found in Scheme 12. The imino compound **24** is reduced, such as with $NaBH_4$, to form the substituted amine **25**.

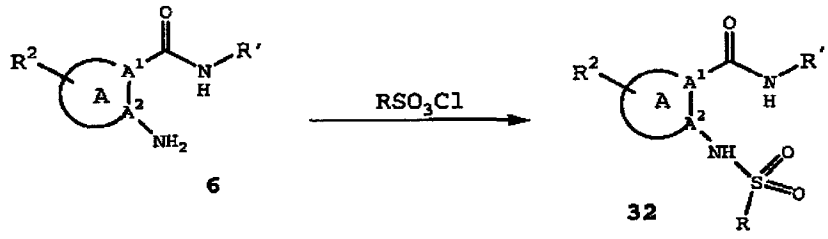
Scheme 13



Substituted pyridines can be prepared by the process outlined in Scheme 13. A solution of sodium hypobromide is freshly prepared and added to 2-hydroxynicotinic acid **26** and heated, preferably at a temperature at about 50°C. Additional sodium hypobromide may be needed to form the bromo compound **27**. The 5-bromo-2-hydroxynicotinic acid **27** is reacted with thionyl chloride, preferably at a temperature >RT, more preferably at about 80°C to form the

2-chloro-nicotinic acid analog **28**. The acid is coupled with an amine, preferably in the presence of EDC, HOBT, and DIEA to form the corresponding substituted amide **29**. Suzuki coupling with the bromo amide and suitable boronic acids, provides the substituted nicotinamide **30**. 2-Amino-nicotinamides **31** are prepared from the corresponding chloro compounds **30** such as by reacting with substituted amines at a suitable temperature, such as about 80°C.

Scheme 14



6 **32**

Sulfonamides **32** can be prepared from amines **6** as shown in Scheme 14. Substituted sulfonyl compounds, such as sulfonyl halides, preferably chloro or bromo, sulfonic acids, an activated ester or reactive anhydride, or in the form of a cyclic amide, and the like, are added to the amine **6** to give the sulfonamide compounds **32**.

The reaction is carried out in a suitable solvent, such as CH_2Cl_2, at a temperature between about RT to about the reflux temperature of the solvent, in the presence of a suitable base, such as DIEA or DMAP.

The amino group of compounds **6** is preferably in free form, especially when the sulfonyl group reacting therewith is present in reactive form. The amino group may, however, itself be a derivative, for example by reaction with a phosphite, such as diethylchlorophosphite, 1,2-phenylene chlorophosphite, ethyldichlorophosphite, ethylene chlorophosphite or tetraethylpyrophosphite. A derivative of

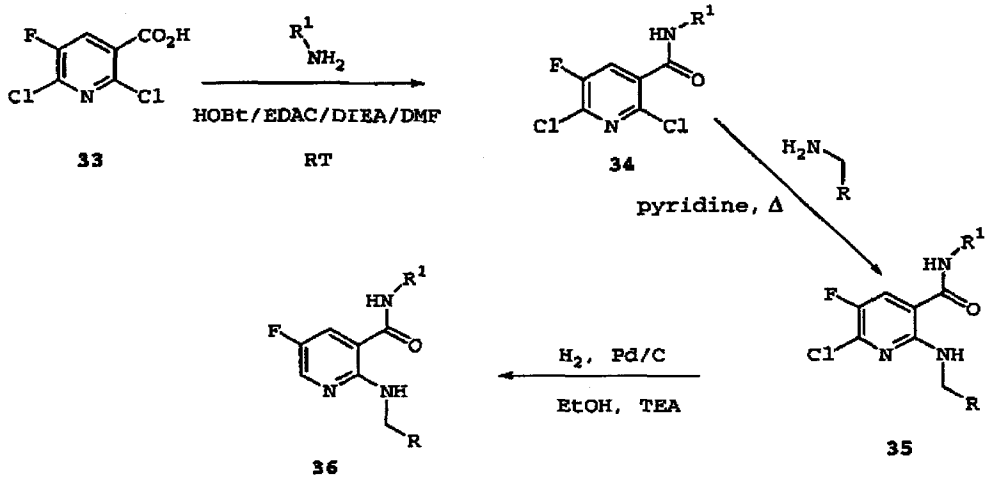
such a compound having an amino group also can be a carbamic acid halide or an isocyanate.

The condensation of activated sulfonic esters, reactive anhydrides or reactive cyclic amides with the corresponding amines is customarily carried out in the presence of an inorganic base, such as an alkaline metal hydrogen carbonate of carbonate, or especially an organic base, for example simple lower $(alkyl)_3$-amines, for example TEA or tributylamine, or one of the above-mentioned organic bases. If desired, a condensation agent is additionally used, for example as described for free carboxylic acids.

The condensation is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example formamide or DMF, a halogenated hydrocarbon, for example CH_2Cl_2, CCl_4 or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example THF or dioxane, an ester, for example EtOAc, or a nitrile, for example CH_3CN, or in a mixture thereof, as appropriate at reduced or elevated temperature, for example in a temperature range of from about -40°C to about +100°C, preferably from about -10°C to about 70°C, and when arylsulfonyl esters are used, also at temperatures of from about 10-30°C, and if necessary under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

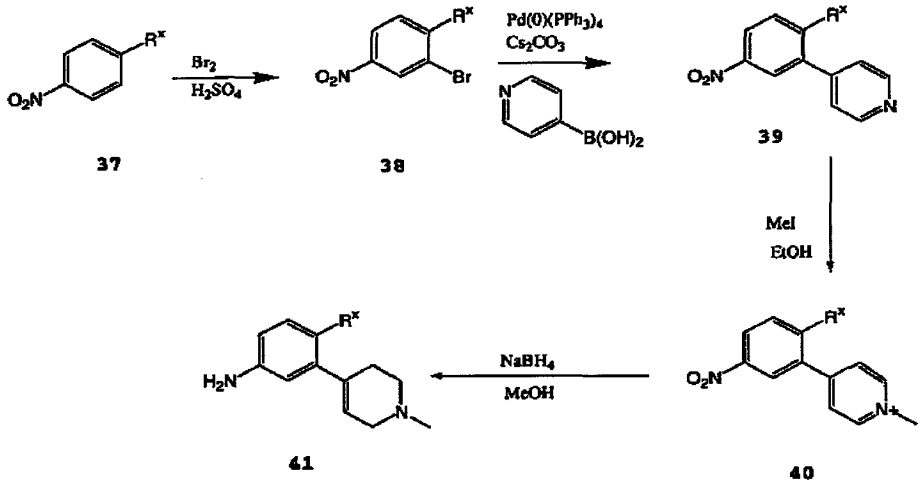
Alcoholic solvents, for example EtOH, or aromatic solvents, for example benzene or toluene, may also be used. When alkali metal hydroxides are present as bases, acetone may also be added where appropriate.

Scheme 15



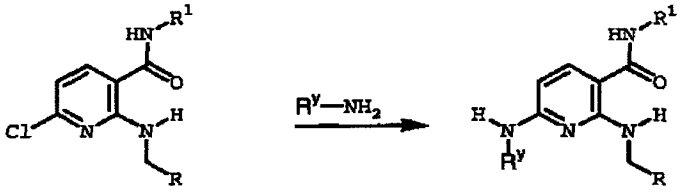
Substituted pyridines can be prepared by the process outlined in Scheme 15. 2-Chloronicotinic acid **33** and substituted amine are coupled under conditions similar to that described in the previous schemes to give the amide **34**. 6-Chloro-2-aminopyridines **35** are prepared from the amide **34**, such as by reacting with substituted amines at a suitable temperature, such as above about 80°C, preferably above about 100°C, more preferably at about 130°C, neat. 6-Chloro-2-aminopyridines **35** are de-chlorinated such as by hydrogenation, for example by treatment with H_2 in the presence of Pd/C, to yield other compounds of the present invention **36**.

Scheme 16



1,2,3,6-Tetrahydro-pyridyl substituted anilines are prepared such as by the procedure described in Scheme 16 (where R^x is a substituent selected from those available for substituted R^1). Nitrobenzenes **37** are brominated, such as with bromine in the presence of acid, H_2SO_4 for example, or with NBS to yield the 3-bromo derivative **38**. Suzuki coupling of the bromo-derivative **38** and a substituted pyridylboronic acid, in an appropriate solvent such as toluene, such as at a temperature above RT, preferably above about 50°C, and more preferably at about 80°C, yields the pyridyl derivative **39**. Alkylation of the nitrophenyl-pyridine **39**, such as by treatment with iodomethane, preferably above about 50°C, and more preferably at about 80°C, yields the pyridinium compound **40**, which upon reduction, such as by $NaBH_4$, yields the tetrahydyropyridine **41**.

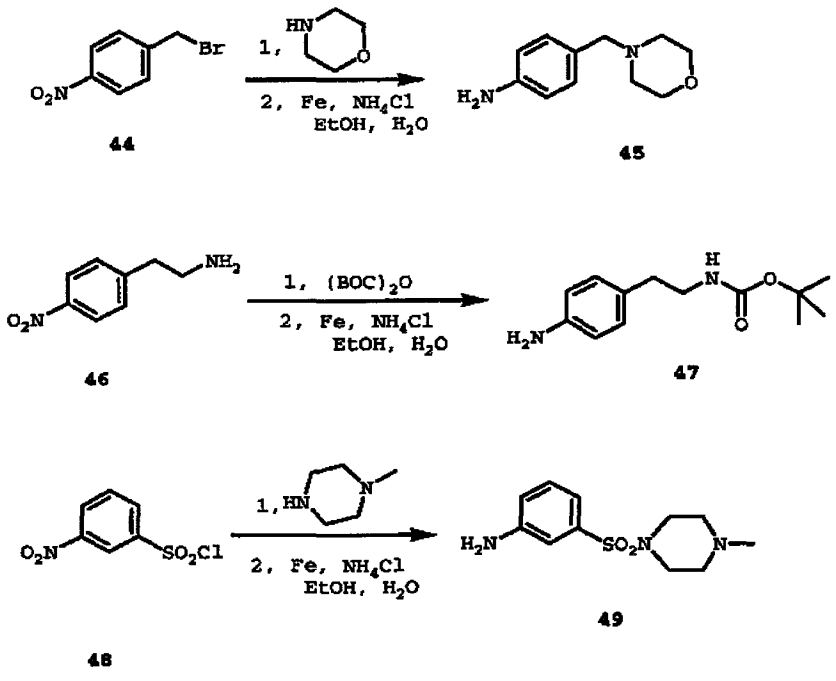
Scheme 17



42 43

6-Amino substituted pyridines are prepared such as by the procedure described in Scheme 17. Similar to the method of Scheme 13, chloropyridine **42** and is reacted with an amine, preferably above about 50°C, and more preferably at about 80°C, to yield the 6-aminopyridines **43**.

Scheme 18



44 45

46 47

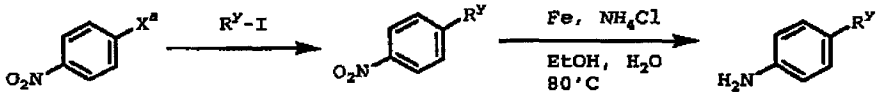
48 49

A series of substituted anilines are prepared such as by the procedure described in Scheme 18. A nitrobenzyl bromide **44** is coupled with morpholine, such as at a temperature at about RT, to yield the heterocyclylmethyl nitrobenzene derivative. Reduction of the nitro compound, such as with iron powder, preferably above about 50°C, and more preferably at about 80°C, yields the heterocyclylmethyl substituted aniline **45**.

Protected alkylamine substituted anilines can be prepared from the nitro free amines **46**, such as with standard protecting agents and chemistry known in the art, such as BOC chemistry. Reduction of the protected nitro compound, such as with iron powder, preferably above about 50°C, and more preferably at about 80°C, yields the aniline **47**.

Sulfonamide substituted anilines can be prepared from nitrobezenesulfonyl chlorides **48**. Coupling of nitrobezenesulfonyl chlorides **48** with reactive heterocyclic compounds, such as substituted piperazines, piperidines, and the like, in a protic solvent such as EtOH, such as at a temperature about RT, yields the nitrobezenesulfonamides **48**. Reduction of the nitro benzenesulfonamide, such as with iron powder, preferably above about 50°C, and more preferably at about 80°C, yields the aniline **49**.

Scheme 19



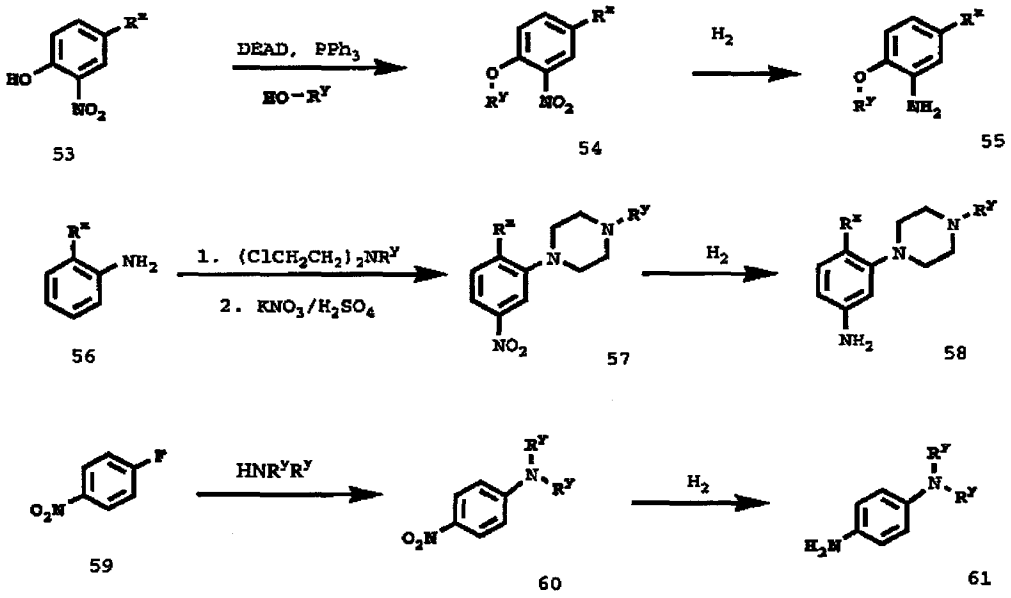
50 **51** **52**

A series of perhaloalkyl-substituted anilines **52**, where R^Y represents perhaloalkyl radicals, are prepared such

as by the procedure described in Scheme 19. 1-Nitro-4-(perfluoroethyl)benzene can be synthesized by the method described in the reference [John N. Freskos, Synthetic Communications, 18(9), 965-972 (1988)]. Alternatively, 1-Nitro-4-(perfluoroalkyl)benzene can be synthesized from the nitro compound, where X^a is a leaving group, such as iodo, by the method described by W. A. Gregory, et al. [J. Med. Chem., 1990, 33, 2569-2578].

Reduction of the nitrobenzenes **51**, such as with iron powder, at a temperature above about 50°C, and preferably at about 80°C, yields the aniline **52**. Hydrogenation, such as with H_2 in the presence of catalyst, such as Pd/C, is also possible.

Scheme 20



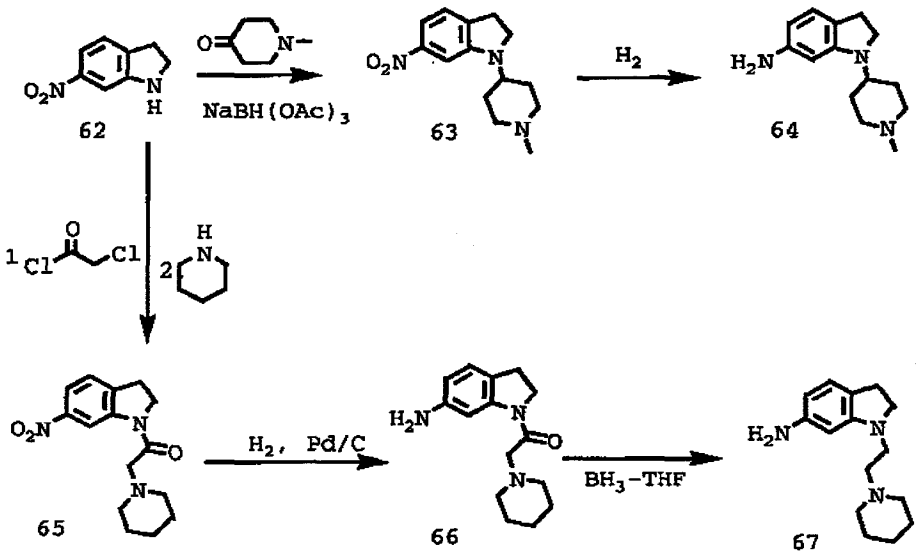
Additional series of substituted anilines are prepared such as by the procedures described in Scheme 20 (where R^x is a substituent selected from those available for substituted R^1). 2-Alkoxy substituted anilines **55** are

prepared from the corresponding phenol compounds **53** such as by the Mitsunobu reaction, including treatment with a N,N-dialkylethanolamine and PPh_3 and DEAD to give the corresponding nitro compound **54**, followed by hydrogenation, such as with H_2 to give the aniline **55**.

Alternatively, piperazinyl substituted anilines **58** can be prepared by the treatment of an aniline **56** with an N-substituted-bis(2-chloroethyl)amine, base, such as K_2CO_3 and NaI, at a temperature above about 50°C, preferably above about 100°C, and more preferably at about 170°C, to give the piperazinylbenzene compound **57**. Nitration, such as with H_2SO_4 and HNO_3, at a temperature above 0°C, and preferably at about RT, followed by hydrogenation, such as with H_2 atmosphere gives the substituted aniline **58**.

Alternatively, piperazinyl substituted anilines **61** can be prepared by the treatment of a fluoro-nitro-substituted aryl compounds **59**. The fluoro-nitro-substituted aryl compounds **59** and 1-substituted piperazines are heated, preferably neat, at a temperature above about 50°C, and preferably at about 90°C, to yield the piperazinyl-nitroaryl compounds **60**. Hydrogenation, such as with H_2 atmosphere in the presence of a catalyst, such as 10% Pd/C, gives the substituted aniline **61**.

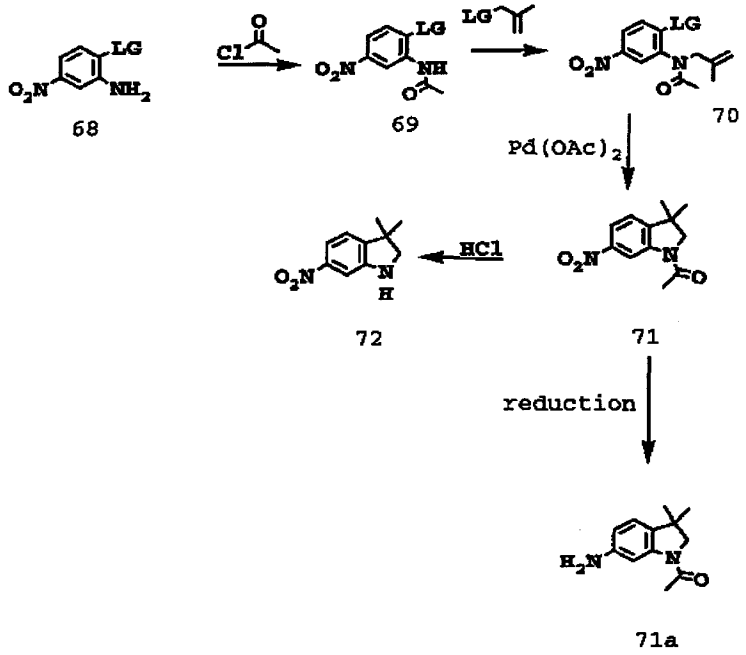
Scheme 21



Substituted indolines are prepared such as by the procedures described in Scheme 21. Substituted amino-indolines **64** are prepared from the nitroindoline **62** and a ketone in the presence of $NaHB(OAc)_3$ to form the 1-substituted indoline **63**. The nitroindoline **63** is hydrogenated, such as with H_2 in the presence of a catalyst, such as Pd/C, to yield the amino-indoline **64**.

Alternatively, substituted amino-indolines **67** are prepared from the nitroindoline **62**. Nitroindoline **62**, is reacted with an acid chloride to form an amide. Further treatment with a primary or secondary amine, preferably a secondary amine, such as in the presence of NaI, at a temperature above about 50°C, and preferably at about 70°C yields the nitroindoline **65**. The nitro compound **65** is hydrogenated, such as with H_2 in the presence of a catalyst, such as Pd/C, to yield the amino-indoline **66**. The carbonyl is reduced, such as with BH_3-THF yields 1-aminoalkyl-indolines **67**.

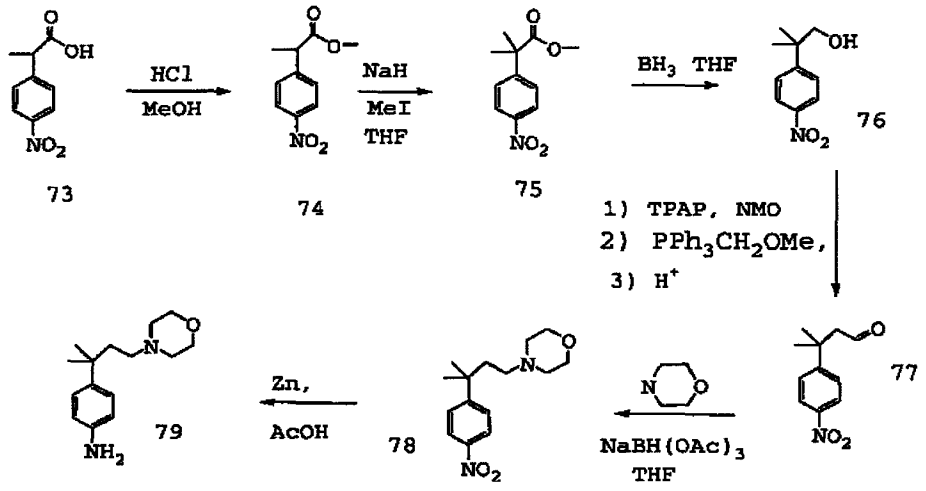
Scheme 22



Substituted indolines are prepared such as by the procedures described in Scheme 22. Substituted acetamides **69** are prepared from the acylation of halo-5-nitroanilines **68** (where LG is bromo or chloro, preferably chloro) with an acylating agent, such as acetyl chloride or acetic anhydride, under standard coupling chemistry, such as with DIEA, and DMAP, at a temperature of about RT, in a suitable solvent, such as CH_2Cl_2, DMF and/or DMAC. The N-(2-methylprop-2-enyl)acetamide **70** is prepared from the acetamide **69**, such as by the treatment of base, such as NaH in anhydrous DMF and a 3-halo-2-methylpropene such as 3-bromo-2-methylpropene or 3-chloro-2-methylpropene, at a temperature between about 0°C and RT, and preferably at about RT; or with $CsCO_3$ at a temperature above RT, preferably above about 50°C and more preferably above about

60°C. Cyclization of the N-(2-methylprop-2-enyl)acetamide **70**, such as by the Heck-type reaction (treatment with $Pd(OAc)_2$ in the presence of base, for example tetraethylammonium chloride, sodium formate, and NaOAc) at a temperature above about 50°C, and preferably at about 80°C, yields the protected (3,3-dimethyl-2,3-dihydro-indol-1-yl)ethanone **71**. Deprotection, such as with strong acid such as AcOH on HCl at a temperature above about 50°C, and preferably at about 70-80°C, yields the 3,3-dimethyl-6-nitro-2,3-dihydro-indol-1-yl **72**. Alternatively, the protected dihydro-6-nitro indoline **71** can be reduced, such as with Fe, or with 10% Pd/C in the presence of an excess of NH_4CO_2H, or with H_2 in the presence of a catalyst to form the protected dihydro-6-amino indoline **71a**.

Scheme 23



Substituted anilines are prepared such as by the procedures described in Scheme 23. Nitrophenyl esters **74** are formed from the acid **73**, such as by treatment with MeOH and acid. Alkylation of the ester **74**, such as by treatment with base, followed by alkyl halide, yields the branched